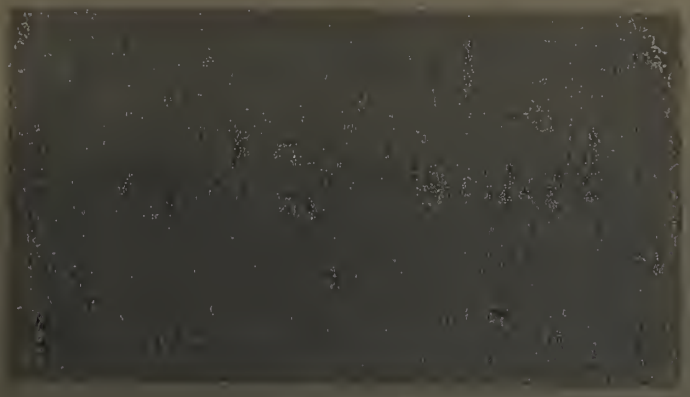

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TERATOGENIC AND CHROMOSOMAL DAMAGING EFFECTS OF ILLICIT DRUGS

An Annotated Bibliography With Selected Related Citations Involving The Effects Of Illicit Drugs

MARCH OF DIMES BIRTH DEFECTS FOUNDATION
White Plains, New York

TERATOGENIC AND CHROMOSOMAL DAMAGING EFFECTS OF ILLICIT DRUGS

An annotated bibliography with
selected related citations
involving the effects of licit drugs

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TERATOGENIC AND CHROMOSOMAL DAMAGING EFFECTS OF ILLICIT DRUGS

An annotated bibliography with
selected related citations
involving the effects of licit drugs

Compiled at the

Addiction Research Foundation Library

by

C. E. Weise

with assistance from

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and edited by

R. J. Hall

Published and Distributed by the

ADDICTION RESEARCH FOUNDATION

Toronto, Ontario, Canada

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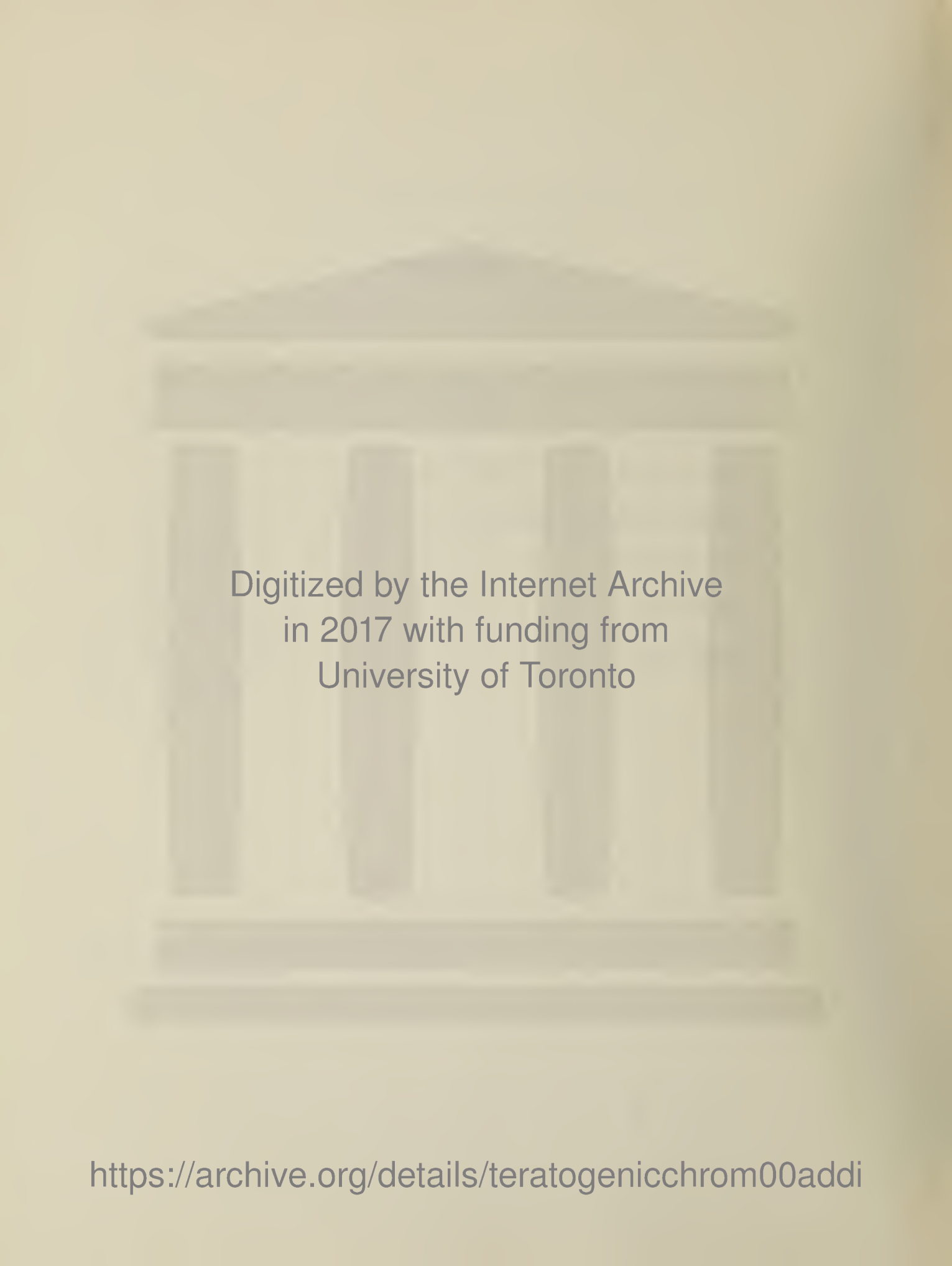
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PREFACE

Teratogenics, or the causing of abnormal development, and chromosomal damage have been and will continue to be topics of importance in our society. Thalidomide, caffeine, aspirin, LSD and a host of other substances have already been linked to chromosomal damage and some have been found to be teratogens.

It would appear to be the case that many members of the drug-using population are either unaware or are unconcerned with the ramifications of the abuse of substances. In point of fact, it would seem as though the drug-user's only concern is with himself and not with the far reaching effects of drug-taking on his family, friends, or offspring.

The compilation of citations in a specific field of interest, such as teratogenic and chromosomal damaging effects of illicit drugs, is a time consuming task, and is not without problems.

The area of first concern is defining the topic or scope of the collection. In the case of this bibliography, it was felt that no comprehensive permanent record of the work performed in this specific area had been completed. The initial thought was to provide an annotated and indexed work restricted to teratogenics and chromosomal damage which occurred as the result of the use of illicit drugs. In the process of collecting the required material, many items were acquired which would not have been included by definition, but which it seemed unfortunate to omit, from the point of view that these articles may aid the researcher or clinician in his study of the topic. It was decided that an indexed listing of these articles would be an appropriate compromise.

A second problem, which usually occurs during the production of any annotated and indexed bibliography is the sheer enormity of the task. For consistency's sake, it is preferable to limit the number of individuals who are involved, but this adds the dimension of fatigue, which may affect quality. Organization of assignments and realistic planning of target dates would be apparent aids to relieving this problem.

The completion of this bibliography marks the third quarter for bibliography production for 1973. During the past 8 months, Solvent Abuse and Interaction of Alcohol and Other Drugs: Supplement I have been published, and once again, it would be remiss not to mention the excellent cooperation and effort extended by each of the Library staff members in making positive contributions, in their own particular fields, to the completion of this volume.

November 1, 1973.
ARF, Toronto

R. J. Hall
Librarian.

INTRODUCTION

Aim

This bibliography was compiled to provide a means of access to a comprehensive collection of papers which have been published concerning the teratogenic and the chromosome-damaging effects of illicit drugs.

The decision was made to index and annotate those articles which dealt specifically with illicit drugs, and to list and index the articles obtained during the collection of the material for the main bibliography, which were concerned with teratogenics and chromosomal damage in general terms and/or dealt with licit drugs. In most cases, the licit drugs were secondarily mentioned in articles in the main bibliography as being taken during the period in which the use of illicit drugs resulted in some detrimental effects to the persons or their newborn.

The range of literature includes research studies, clinical reports, review articles, letters to the editor, and commentaries of all types.

Types of Information

A. Citations

Items are arranged alphabetically by senior author. The references include the usual bibliographic data, as well as index terms and an accession (microfiche) number. As previously mentioned, the items in the first section also include a short annotation.

B. Key Word Index

An alphabetical key word listing (pages 155-156) permits the user to select the terms which are relevant to his needs. The number beside each key word refers him to the Key Word Index (pages 157-163) where terms are grouped under appropriate headings accompanied by a list of corresponding bibliography numbers or appendix numbers (prefaced with the letter A) which directs him to the appropriate citations.

C. Author Index

The name of each author represented in the bibliography is listed alphabetically (pages 165-172), and the citation numbers follow. An underlined number indicates that the author is the senior author for the particular item. Again, the appendix citation numbers are prefaced with the letter A.

D. Drug Index

Drugs which are discussed in the cited articles are listed alphabetically with corresponding numbers (bibliography and/or appendix) on pages 173-175, along with appropriate cross references.

E. Language Abbreviations

The first item of the key word section of each citation represents the language of the paper. The following are the abbreviations which have been used:

C - Czechoslovakian
D - Dutch
Da - Danish
E - English
F - French
Fi - Finnish
G - German
I - Italian
J - Japanese
N - Norwegian
Po - Polish
S - Swedish
Sp - Spanish

Using the Indexes

To facilitate the combination of indexing terms, it is often helpful to photocopy the page containing one of the chosen terms and use it to compare (by circling relevant numbers) with the numbers listed beside the second term.

It is important to remember that sequential numbering is represented by a hyphen. For example, 122-125 represents citation numbers 122, 123, 124 and 125.

1. Aase, J. M., Laestadius, N., and Smith, D. W.
CHILDREN OF MOTHERS WHO TOOK L. S. D. IN PREGNANCY.
Lancet, 2(7663): 100-101, 1970.
E - lett. ed. - in vivo - gen. disc. - tables - humans - female - chromosome damage - teratogenicity - intent. use - oral admin. - single dose - extended use - female consumpt. - stage of devel. - chrom. aberr. - congenit. defects - premature birth - no effect - birth, full term - chrom. analysis B-1257.

This letter gives reference to five studies on the teratogenesis and the chromosomal damage ability of LSD. It presents in table form the results of a study of ten babies whose mothers had ingested LSD at different times during their pregnancies. No evidence of any positive drug effect was detected although three of the babies were born prematurely and all the babies were girls.

2. Abbo, G., Norris, A., and Zellweger, H.
LYSERGIC ACID DIETHYLAMIDE (LSD-25) AND CHROMOSOME BREAKS.
Humangenetik, 6(3): 253-258, 1968.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - therapeut. use - oral admin. - extended use - female consumpt. - male consumpt. - chrom. aberr. - chrom. analysis - lab. test. B-2651.

The authors undertook an in vivo study to determine the chromosomal damage capabilities of LSD. Nine psychiatric patients who had been treated from 9 to 41 months previously with the drug, a married couple who had ingested LSD an indefinite number of times, and the latter's child were used in comparison with 32 control subjects. The results showed a significantly greater number of chromosomal breaks in the leukocytes and fibroblasts of the drug users over the controls. Chromatid breaks were more frequent while isochromatid breaks and secondary constrictions were no more frequent than in the control group. The authors discuss the possible consequences of chromosome breaks in general and remark on the critical organogenetic period of pregnancy. It is stated that LSD could have a similar teratogenic effect as thalidomide if ingested during this period.

3. Alexander, G. J., Miles, B. E., Gold, G. M., and Alexander, R. B.
LSD: INJECTION EARLY IN PREGNANCY PRODUCES ABNORMALITIES IN OFFSPRING OF RATS.
Science, 157: 459-460, 1967.
E - res. pap. - in vivo - rats - teratogenicity - exper. admin. -

s. c. admin. - single dose - female consumpt. - stage of devel. - abort. rate - death - fetocidal - litter - birth, full term B-2652.

A series of three in vivo experiments were conducted with rats to study the teratogenesis of a single subcutaneous injection of LSD administered either early or late in the pregnancy. The dose which was used was thought to correspond to the hallucinogenic dose for man of 100 to 400 μg./person. Of the ten rats injected on the fourth day of pregnancy, two aborted, offspring of four were stillborn (some being stunted), one delivered a litter of seven healthy rats and one underdeveloped, the eighth gave an abnormally small litter of four pups, and the other two delivered normal litters. In contrast, the offspring of the controls and the rats injected from days 7 to 16 of gestation appeared healthy. It was apparent from the gross examinations of the young that there was a decreased rate of development in some of those of LSD treated mothers.

4. Alexander, G. J.
LSD: EFFECTS ON OFFSPRING.
Science, 158(3800): 522, 1967.
E - lett. ed. - gen. disc. - rats - teratogenicity - exper. admin. - s. c. admin. - female consumpt. - stage of devel. - no effect B-2653.

This letter is a reply to a critique by J. A. DiPaolo (Science, 158: 522, 1967). The author states that the purpose of his earlier research paper (Science, 157: 459-460, 1967) was to report the damage to the offspring of rats injected early in pregnancy with LSD. He states that his further investigations seem to confirm his earlier results.

5. Alexander, G. J., Machiz, S., and Alexander, R. B.
INHERITED ABNORMALITIES IN THREE GENERATIONS OF OFFSPRING OF LSD-TREATED RATS.
Federation Proceedings; Federation of American Societies for Experimental Biology, 27(2): 220, 1968.
E - abst. - in vivo - rats - teratogenicity - exper. admin. - abort. rate - death - fetocidal - birth, full term B-2654.

LSD caused teratogenic effects in rats when administered early in pregnancy which carried over four generations. Thirteen of 29 pregnancies in 2nd generation LSD rats were abnormal, consisting of three abortions, three deaths during or after gestation, and seven litters with some stillborn or stunted young. When both 2nd generation parents were offspring from treated females, 70 percent

of their pregnancies were abnormal. When only one parent was from treated females, 32 percent of the pregnancies were abnormal. Thirty-two 4th generation pups were either stillborn or died shortly after birth.

6. Alexander, G. J., Gold, G. M., Miles, B. E., and Alexander, R. B.
LYSERGIC ACID DIETHYLAMIDE INTAKE IN PREGNANCY: FETAL DAMAGE IN RATS.
Journal of Pharmacology and Experimental Therapeutics, 173(1): 48-59, 1970.
E - res. pap. - in vivo - tables - rats - teratogenicity - exper. admin. - oral admin. - s. c. admin. - single dose - female consumpt. - dose/response - stage of devel. - abort. rate - congenit. defects - death - fetal maldevel. - fetocidal - litter - resorpt. rate - autop. - birth, full term B-2655.

A series of in vivo experiments was undertaken to study the fetal damage caused by subcutaneously and orally administered LSD in rats. The dose ranged from 5 μg./kg. to 100 μg./kg. and was given once to each animal between the first and 16th days of gestation during its first, second, or third pregnancy. Fifty-five females were given the drug early in pregnancy and a set of tables presents the results as to the number of resorptions, deaths, and abnormal pregnancies, as well as the effects upon the litters. It was found that 47 percent of all the females treated with LSD had abnormal pregnancies as compared to 15 percent of the control female rats. In addition, 11 percent of the offspring from the treated females were damaged. The surviving offspring were allowed to mature and were mated with offspring of the controls and of the other LSD treated rats. It was found that there was a higher rate of death and abnormal pregnancies with the 2nd generation rats of the females that had been treated with LSD. There was no difference in effect between the two routes of administration and LSD, administered after the 8th day of gestation, had little effect on the litter and the offspring.

7. Amarose, A. P., and Schuster, C. R.
CHROMOSOMAL ANALYSES OF BONE MARROW AND PERIPHERAL BLOOD IN SUBJECTS WITH A HISTORY OF ILLICIT DRUG USE.
Archives of General Psychiatry, 25(2): 181-186, 1971.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - chrom. aberr. - chrom. analysis - chrom. analysis, peripheral - chrom. analysis, bone mar. - confound. agent. B-2656.

Former illicit drug users staying at a therapeutic residential house were studied to determine if their previous drug use had caused any lasting chromosome damage. Bone marrow and peripheral blood chromosomes were studied and counted. Of 2,269 bone marrow cells, 4.5 percent had abnormal metaphases while 20.1 percent of 2,237 peripheral blood cells had abnormal metaphases. This latter percentage was significantly larger than that found in the controls. Damage to the chromosomes was of a random nature and no marker or standard karyotype was found. The cells did not deviate greatly from the normal number of 46 chromosomes. The subjects had been placed into one of four groups according to the drugs they used the most; amphetamines, barbiturates, opiates, and psychedelics. No correlation was found between these individual groups and the chromosome damage found.

8. Anonymous
A GENETIC TRIP.
Journal of the American Medical Association, 204(3): 259-260, 1968.
E - gen. pap. - review - humans - chromosome damage - teratogenicity - chrom. aberr. - no effect B-2657.

The author states that the teratogenicity and the chromosome damaging effect of LSD are the first physically harmful effects associated with hallucinogens that have been reliably found. He cites the papers of M. M. Cohen et al. and of other writers outlining what the different groups of researchers have found in connection with chromosome aberrations and congenital defects. The drug chlorpromazine was found to be used by some of the LSD users who had been studied. The recommendation is made that the chromosome damaging effects of chlorpromazine, as well as marijuana, amphetamines, barbiturates, cocaine, and other drugs, be investigated apart from the effects of LSD.

9. Anonymous
CANNABIS IN EARLY PREGNANCY.
Bulletin on Narcotics, 20(2): 8, 1968.
E - abst. - mice - teratogenicity - exper. admin. - i.p. admin. - single dose - extended use - fetal maldevel. - resorpt. rate - no effect B-2658.

The results of an experiment by Persaud and Ellington are presented. The researchers found that foetuses of pregnant mice treated on day 6 of gestation with a single intraperitoneal dose (16 mg./kg.) of cannabis resin had a high rate of over-all stunting. No other

effects were found. When the same dose was given daily from day 1 to 6 of gestation, complete foetal resorption took place.

10. Anonymous
CANNABIS - YET ANOTHER TERATOGEN?
British Medical Journal, 1(5647): 797, 1969.
E - gen. pap. - sec. disc. - teratogenicity - i. p. admin. - no effect B-2659.

Since the thalidomide tragedy, a fair number of substances have been proven teratogenic to the offspring of laboratory animals. The new substance that is now to be added is the extract of cannabis which was injected intraperitoneally into the pregnant females. It is unfortunate that at present, a potentially therapeutic drug would be kept off the market if it caused congenital defects in the young of pregnant rodents. This practice, if it had applied in the past, would have prevented the widespread use of insulin, penicillin, aspirin, and other beneficial drugs. The addition of cannabis to the list of teratogens only provides one more argument against the abuse of this substance.

11. Anonymous
CHROMOSOMENSCHÄDEN DURCH LSD? [Chromosome lesions due to LSD?]
Deutsche Medizinische Wochenschrift, 96(4): 181 1971.
G - abst. - plants - chromosome damage - exper. admin. - chrom. aberr. - chrom. analysis B-2660.

The author summarizes the work done by Singh, M. P., et al. (Science, 169: 491, 1970). Barley was subjected to a 25 μg./ml. solution of LSD for 4 to 8 hours, after which the root tips were histologically examined. The results indicated that in the experimental group, 38 to 56 percent of all the cells had chromosomal damage (mostly breakage) as opposed to up to 1.6 percent in the LSD-free group.

12. Anonymous
CLINICAL VALUE OF LSD QUESTIONED; PHYSICAL DAMAGE REPORTED.
Journal of the American Medical Association, 201(13): 24, 1967.
E - gen. pap. - gen. disc. - humans - chromosome damage - intent. use - female consumpt. - no effect B-2661.

The author states that LSD has come under the scrutiny of most of

the pertinent disciplines of research. There are now indications that the substance is physically damaging in that it has been found to be associated with increased chromosome breakage. It also has been shown that LSD crosses the placenta. No congenital defects have been connected with LSD use. The recommendation is made that LSD should not be used during a patient's reproductive years without a sound medical reason.

13. Anonymous
EFFECT OF LSD ON CHROMOSOMES.
Canadian Medical Association Journal, 98: 221-222, 1968.
E - gen. pap. - gen. disc. - humans - chromosome damage - teratogenicity - exper. admin. - intent. use - extended use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - no effect B-2662.

Chromosomal mutations occur in LSD users at a rate of two to four times that which is found in control subjects and mutations have also been found in cells exposed to LSD in vitro. Chromosomes of infants of mothers who had taken LSD in pregnancy have also been damaged. Changes consist of chromatid and isochromatid breaks and resemble those following radiation and some viral infections. These breaks result in reciprocal translocations and possibly, polyploidy. Risk to offspring is not established but stillbirths and congenital defects reported in exposed laboratory animals are suggestive. Reference to the first reported case where LSD may have cuased a gross fetal abnormality (unilateral fibular aplastic syndrome) is given. The mother took LSD three times during her pregnancy and the father had also taken it. Chromatid breaks were seen in the cells of both the parents and the child.

14. Anonymous
HALLUCINOGEN AND TERATOGEN?
Lancet, 2(7514): 504-505, 1967.
E - gen. pap. - gen. disc. - humans - chromosome damage - exper. admin. - intent. use - single dose - female consumpt. - chrom. aberr. - congenit. defects - no effect B-2663.

The author feels that most LSD advocates would admit that some users could suffer serious psychiatric damage. In addition, there now seems to be evidence that LSD can increase chromosomal abnormalities, particularly to chromosome number one, in cultured human leucocytes from normal subjects. This effect seems to be related to the length of the exposure and the dose. A schizophrenic who had been treated over six years with a total of 2505 μg. of LSD

had a chromosome-breakage rate much higher than normal and had changes that did not appear in 35 schizophrenics not treated with LSD. A "quadriradial" formation was observed between two no. 1 chromosomes. Studies have shown congenital defects in newborns of humans and laboratory animals who had taken LSD. This substance must be considered as a possible cause when a deformed child is born.

15. Anonymous
HALLUCINOGENS AND NARCOTICS ALARM PUBLIC.
Chemistry and Engineering News, 48(47): 44-45, 1970.
E - gen. pap. - sec. disc. - chromosome damage - teratogenicity - no effect - drug action B-2664.

The author discusses the drug action of some of the most abused hallucinogens and narcotic analgesics. There have been no human deaths directly related to an LSD overdose. The physiological toxicity appears to be low. The finding of the Canadian Commission of Inquiry into the Nonmedical Use of Drugs was that the research into the teratogenic effect of LSD has given confusing results. Deformities are found in the offspring of some animals, after high doses of the substance are given early in pregnancy, but not in other animals. After absorption, LSD is concentrated in the liver while relatively little reaches the brain despite the fact that LSD easily penetrates the brain and readily crosses the placenta.

16. Anonymous
LEGALIZE MARIHUANA?
Medical Journal of Australia, 1(25): 1237-1238, 1970.
E - gen. pap. - sec. disc. - humans - mice - rats - teratogenicity - congenit. defects - fetal maldevel. - resorpt. rate - no effect B-2665.

The author deals with some of the arguments for not legalizing marijuana by reporting the findings of different researchers who have presented papers in these areas. Studies are cited which have shown the species-specific teratogenic properties of marijuana in mice and rats. Resorption of foetuses, stunted, and deformed foetuses were found. A case is reported of a child born lacking its right hand. The mother had infrequently taken LSD and had smoked marijuana throughout the pregnancy. Since no chromosomal aberrations were found, LSD was ruled out as the causal agent. From these studies, the possibility of marijuana having a teratogenic effect is raised.

17. Anonymous
LE POUVOIR TÉRATOGÈNE DU LSD. [The teratogenic power of LSD.]
Presse Médicale, 75(37): 1858, 1967.
F - gen. pap. - gen. disc. - review - humans - rats - chromosome damage - teratogenicity - exper. admin. - intent. use - female consumpt. - chrom. aberr. - fetal maldevel. - fetocidal - carcinogen. effect - litter - no effect B-2666.

A brief review is presented of the developments in the research of the effects of LSD on chromosomes. There does not seem to be any doubt that the use of LSD, even if only occassional, results in alteration of the leucocytic chromosomes. Fetal malformations, abortions, and neonatal mortality have been reported as being caused by LSD in studies with laboratory animals. There is still controversy over the establishment of a cause and effect relationship between the use of LSD and fetal malformations in humans. The author also notes the growing use of STP among the "hippies" of North America.

18. Anonymous
LEUKAEMIA AND L. S. D.
British Medical Journal, 2(5660): 775-776, 1969.
E - gen. pap. - gen. disc. - humans - chromosome damage - chrom. aberr. - carcinogen. effect - no effect B-2667.

On the basis of one case, the author feels that there is possibly a causal relationship between LSD and leukemia. Reference is made to reports of LSD inducing chromosome damage in vitro and in vivo in humans (including infants whose mothers took it during pregnancy) and in animals. Reports are cited of congenital defects in animals and in two infants whose parents had taken LSD. Other work suggests that there exists a repair mechanism, and that the damage is only transitory. As to its therapeutic benefits in psychiatry, contradictory results have been found. The risks of psychosis or teratogenesis should be weighted against the possible therapeutic gain.

19. Anonymous
L. S. D. AND CHROMOSOMES.
British Medical Journal, 4(5572): 124-125, 1967.
E - gen. pap. - gen. disc. - humans - chromosome damage - chrom. aberr. - congenit. defects - no effect B-2668.

The toxic effects of LSD are not well known although the substance

is used in therapy and for illicit self-administration. Genetic effects were reported by Cohen et al. from in vitro tests and from one in vivo study with a human. The chromosome aberrations included acentric and dicentric fragments, chromatid breaks and exchanges. LSD had similar effects on two drug users who became patients with chronic myeloid leukemia and had Ph^1-like chromosomes. In laboratory studies, it caused abortions, stillbirths, congenital defects, and reduced litter size in rats injected early in pregnancy. LSD is not only a potential risk to the mind but may also cause chromosomal and foetal abnormalities, and possibly, leukemia. Screening of more drugs for their teratogenic, chromosome breaking, and mutagenic potential is urged with the use of in vitro techniques now available.

20. Anonymous
L. S. D. AND CHROMOSOMES.
British Medical Journal, 2(5608): 778-779, 1968.
E - gen. pap. - gen. disc. - humans - mice - rabbits - rats - chromosome damage - teratogenicity - exper. admin. - intent. use - chrom. aberr. - congenit. defects - no effect B-2669.

Chromatid aberrations have been reported in LSD users and in children exposed in utero early in pregnancy. A Ph^1-like chromosome, which has been found in some cases of leukemia, has also been found in two LSD users. Two parents who had used LSD were found to have chromosomal aberrations and had a child with congenital defects. A causal relationship is still in need of confirmation. Reports that are cited are often contradictory and inconclusive. The dose used and the use of other drugs are often unreliably reported. LSD added to cultures in vitro induces breaks in chromosomes but so do aspirins and other drugs. Potential teratogenic effects have also been studied in rats, mice, rabbits, and hamsters with varied results. There was no effect found with rabbits. Better controlled studies to evaluate these properties of LSD are essential as it is used both therapeutically and illicitly.

21. Anonymous
MARIJUANA AND HEALTH: A REPORT TO THE CONGRESS.
American Journal of Psychiatry, 128(2): 189-193, 1971.
E - gen. pap. - sec. disc. - rats - teratogenicity - no effect - drug action B-2670.

The author discusses the many aspects of marijuana use under the headings "Subjective Effects", "Physiological Effects of Acute Use", "Acute Psychotic Episodes", "Intellectual and Motor Performance",

"Marijuana and Birth Defects", "Effects of Long-Term Chronic Use", "Marijuana and the Use of Other Drugs", and "Future Research Directions". It is stated that there is little evidence that marijuana is teratogenic. Preliminary findings which have shown a teratogenic effect in laboratory animals with large doses of this substance have been found to be unreplicable. Nevertheless, the use of marijuana during pregnancy is particularly unwise.

22. Anonymous
RADIOMIMETIC PROPERTIES OF LSD.
New England Journal of Medicine, 277(20): 1090-1091, 1967.
E - gen. pap. - gen. disc. - humans - chromosome damage - oral admin. - single dose - extended use - chrom. aberr. - no effect - chrom. analysis - chrom. analysis, peripheral B-2671.

The author expresses the importance of the cultured peripheral lymphocyte technique in protecting people from the effects of drugs, chemicals, and radiation. This technique is the observation of chromosomes from cultured human peripheral lymphocytes. LSD is being scrutinized in such a manner to determine its chromosome damaging effect. Due to its long lasting effects on chromosomes, LSD seems to be highly radiomimetic. An LSD user may experience somatic mutations and cell depletion comparable to a dose of 25 to 50 R. per day of chronic wholebody gamma radiation. From this, the chance that more sensitive tissues and cell types, such as spermatogonia, may be damaged requires immediate investigation. The teratogenic effect of LSD has recently been confirmed in rodent fetuses.

23. Anonymous
TERATOGENIC PROPERTY OF LSD.
Bulletin on Narcotics, 20(2): 8, 1968.
E - abst. - rats - teratogenicity - congenit. defects - no effect B-2672.

Chromosome abnormalities have been found in cells cultured with LSD. Also, one group of researchers found that an injection of 5 mg/kg of body weight of LSD on the fourth day of pregnancy in rats may cause abortions and malformations in the offspring. This dose is comparable to the human hallucinogenic dose (1.7 to 6.7 mg/kg). The significance and the effects of chromosome breaks are unknown but Zellweger et al. report presumptive evidence that LSD, taken during the organogenetic period of pregnancy, may have a teratogenic effect in humans.

24. Assemany, S. R., Neu, R. L., and Gardner, L. I.
DEFORMITIES IN A CHILD WHOSE MOTHER TOOK L. S. D.
Lancet, 1(7659): 1290, 1970.
E - lett. ed. - case rep. - humans - male - teratogenicity - intent. use - female consumpt. - congenit. defects - birth, full term
B-2674.

A case report is given of an infant who had amputation deformities of the third finger of the right hand and the third toe of the left foot and whose mother had used LSD during pregnancy. The mother was 22 years of age and had had an apparently normal child born in the past. The amount of LSD taken could not be determined and there were three episodes of hepatitis during the pregnancy. There was no evidence of chromosomal damage in either the mother or the child. The child's deformities compare to a previously reported case of a child whose mother had used LSD during pregnancy but are in contrast to deformities caused by thalidomide which affects the left limbs more severely than the right.

25. Auerbach, R., and Rugowski, J. A.
LYSERGIC ACID DIETHYLAMIDE: EFFECT ON EMBRYOS.
Science, 157(3794): 1325-1326, 1967.
E - res. pap. - in vivo - tables - mice - teratogenicity - exper. admin. - i. p. admin. - stage of devel. - embryo. maldevel. - birth, pre term. B-1210.

LSD caused a 57 percent incidence of grossly abnormal embryos when it was injected intraperitoneally in mice before day 7 of pregnancy (equivalent to days 16 to 22 in humans). In all cases, the malformations involved characteristic brain defects (photos included). Neural structures are first being formed at this time. It cannot be determined whether the ineffectiveness of LSD given on days 8 and 9 of pregnancy is due to specific action of LSD or to increased resistance to teratogenesis in general. Abnormalities of the lower jaw, eye positions, and facial contour also occurred. Based on body weight, the dose was less than an average single exposure in man. The findings support those of other researchers working with rats.

26. Auerbach, R.
LSD: TERATOGENICITY IN MICE.
Science, 170(3957): 558, 1970.
E - lett. ed. - gen. disc. - mice - teratogenicity - exper. admin. - injection - congenit. defects - no effect B-2675.

The author repeats his findings that injected LSD causes defects in mouse embryos. He cites his, and two other reports, to oppose the negative results found by Roux et al. in mice, rats, and hamsters. LSD appears to induce an increased incidence of those defects which also occur spontaneously in inbred lines. But it has been found that teratogens always act against a background of genetic predisposition. This does not discount the evidence that LSD is a potential teratogen in mice.

27. Baker, P. C.
LSD: ITS EFFECT UPON 5-HYDROXYTRYPTAMINE IN EMBRYONIC DEVELOPMENT OF XENOPUS LAEVIS.
Experientia, 27(5): 536-537, 1971.
E - res. pap. - in vivo - amphibians - teratogenicity - exper. admin. - single dose - stage of devel. - embryo. maldevel.
B-2676.

The author undertook an experiment to determine if LSD could cause biochemical abnormality in developing embryos. The 5-hydroxytryptamine level in embryos of the South African Clawed Toad was measured after receiving a concentration of 0.06 mg./ml. of aquarium water of LSD for 6 hours. No observable morphological or behavioral errors were observed in the embryos at this dosage. The whole embryo 5-hydroxytryptamine levels were affected but only at the neurula (or stage 19 of development) exposure period. This effect was not transitory in nature as it was demonstrable 5 and 7 days following LSD administration. There is evidence that abnormal 5-hydroxytryptamine metabolism interferes with normal development. Although unsubstantiated, this could possibly be the mechanism for the teratogenic effect of LSD.

28. Baker, P. C.
THE EFFECTS OF LSD ON INDOLEAMINE ENZYMES IN EMBRYONIC XENOPUS LAEVIS.
Comparative and General Pharmacology, 3(9): 22-26, 1972.
E - res. pap. - in vivo - tables - amphibians - exper. admin. - single dose - stage of devel. - embryo. maldevel. B-2677.

In his previous paper (Experientia, 27(5): 536-537, 1971), the author found changes in the 5-hydroxytryptamine levels in embryos exposed to LSD. The present experiment was undertaken with the embryos of the South African Clawed Toad to determine if the previous changes were due to variations in the enzymatic action occurring in the embryos. Groups of embryos were exposed to LSD for 6 hours at a concentration of 0.06 μg./ml. of aquarium water. The

two stages for exposure were the neurula (stage 19) and the post-hatching (stage 40). The activities of the enzymes 5-hydroxy-tryptophan decarboxylase, monoamine oxidase, and hydroxyindole-O-methyltransferase were measured in the whole body and the brain after the pre-metamorphic stage of development. The results showed a comparable reduction in the first two enzymes mentioned which should possibly cancel each other's effect and result in an unaltered 5-hydroxytryptamine level. Since this is not the case, the effect of LSD upon 5-hydroxytryptamine cannot be explained in terms of the altered activity of these two enzymes. The activity of hydroxyindole-O-methyltransferase is reduced after post-hatching exposure but it remains unclear if this variation is connected to the reduction in the 5-hydroxytryptamine level.

29. Barnett, B. M., and Muñoz, E. R.
GENETIC EFFECTS OF LSD IN DROSOPHILA MELANOGASTER SPERM.
Mutation Research, 11(4): 441-444, 1971.
E - res. pap. - in vivo - tables - fruit flies - chromosome damage - exper. admin. - injection - single dose - male consumpt. - dose/response - chrom. aberr. - spermatogen. effect - chrom. analysis B-2678.

This paper deals with sex-linked recessive lethals and II-III translocations tests in fruit fly mature sperm. Six day old males were injected intraabdominally with a dose of 0.4 µl. of LSD. The males were mated either immediately after the treatment or 24 hours after treatment. The results of the sex-linked recessive lethal tests were that among the total progeny of the males mated immediately, 27 lethals from 8517 chromosomes tested were found. This was significantly greater than normal. Four lethals were found from 4190 chromosomes tested from the progeny of the males mated 24 hours after treatment. No II-III translocations, which would indicate chromosome breakage, were detected in the 1300 chromosomes analyzed.

30. Beall, J. R.
A TERATOGENIC STUDY OF CHLORPROMAZINE, ORPHENADRINE, PERPHENAZINE, AND LSD-25 IN RATS.
Toxicology and Applied Pharmacology, 21(2): 230-236, 1972.
E - res. pap. - in vivo - rats - teratogenicity - exper. admin. - oral admin. - single dose - female consumpt. - congenit. defects - fetal maldevel. - resorpt. rate - birth, pre term. B-2679.

Chlorpromazine hydrochloride, orphenadrine hydrochloride,

perphenazine, and LSD were administered by esophageal intubation to different groups of female rats. Each drug was administered in three different dose levels with no concentration exceeding 2.5 ml. The females were bred and on day 21 of gestation, they were sacrificed and the offspring removed. Orphenadrine was the only drug to produce abnormal offspring in some pregnant rats. However, all four influenced, to varying degrees, resorptions and offspring body weights. Statistics and tables of the results are given. Chromosome analyses were not performed. None of the 680 young of the LSD treated females were grossly deformed. Higher doses of perphenazine and chlorpromazine were lethal to some treated females but no teratogenic effects were found in these groups. Less toxic doses of orphenadrine caused some visceral changes in the offspring.

31. Becker, C. E.
THE CLINICAL IMPORTANCE OF PHARMACOGENETICS.
California Medicine, 111(4): 291-297, 1969.
E - gen. pap. - sec. disc. - humans - chromosome damage - chrom. aberr. - no effect B-1426.

The author discusses "pharmacogenetics" or the study of genetically determined variants where the phenotype or the genotype are detected by drug effects. Seemingly, only recently has it been appreciated that genetic factors may have a large part in drug-patient variation. In the few paragraphs in which the author discusses LSD, he points out that LSD cannot be specifically implicated in causing chromosome damage. There have only been a limited number of studies and other drugs may have been influential. The most disturbing fact about LSD is that it causes unusual types of breaks rarely observed in normal persons. It is called the quadriradial breakage pattern.

32. Bender, L., and Siva Sankar, D. V.
CHROMOSOME DAMAGE NOT FOUND IN LEUKOCYTES OF CHILDREN TREATED WITH LSD-25.
Science, 159(3816): 749, 1968.
E - lett. ed. - in vivo - humans - chromosome damage - therapeut. use - extended use - chrom. aberr. - no effect - chrom. analysis B-1222.

A report of chromosome breaks in 6 of 8 users of LSD compared to 1 of 9 non-users prompted this study on chromosomes in 27 children in a State hospital. Of the seven schizophrenics treated with LSD, two showed chromosome breakage while five had normal

karyotypes. At least ten metaphases were counted for each patient. The twenty other schizophrenics were normal. The negative findings are significant in as much as the children received up to 500 μg. per day of pure LSD for as long as 3 years.

33. Berger, R.
LSD-25 ET ANOMALIES GÉNÉTIQUES. [LSD-25 and genetic anomalies.]
Presse Médicale, 79(41): 1779-1780, 1971.
F - gen. pap. - review - humans - mice - mammals - plants - rabbits - rats - chromosome damage - teratogenicity - female consumpt. - congenit. defects - death - carcinogen. effect - no effect - confound. agent B-2680.

A review of the literature is presented on the mutagenic, carcinogenic, and the teratogenic properties of LSD. The author notes the various results obtained from experiments with humans, animals, and plants. Cohen et al. brought attention to the possibility of producing chromosome anomalies in vitro with LSD. The experiments which followed failed to show uniform results, perhaps because of the number of variables involved in the action of LSD-25 in the organism. The author warns of the danger of comparing one species against another and concludes with Dishotsky's thought that there are no contraindications (except in the case of pregnancy) for the controlled use of LSD.

34. Berlin, C. M., and Jacobson, C. B.
CONGENITAL ANOMALIES ASSOCIATED WITH PARENTAL LSD INGESTION.
Pediatric Research, 4(4): 377-378, 1970.
E - abst. - in vivo - humans - teratogenicity - intent. use - female consumpt. - abort. rate - congenit. defects - birth, full term - chrom. analysis, peripheral - confound. agent B-1221.

A prospective study of 124 pregnancies was undertaken to evaluate the reproductive effects of LSD. Pregnant women were admitted to the study when previous LSD use was proven. There was a total 65 abortions and 59 live births. Four of 14 abortuses showed severe congenital defects. Six infants of the 59 had severe congenital anomalies. Although the mothers' social and physical conditions could have been influential, the possibility of LSD as a mutagen must be seriously considered.

35. Berlin, C. M., and Jacobson, C. B.
PSYCHEDELIC DRUGS - A THREAT TO REPRODUCTION?
Federation Proceedings; Federation of American Societies for Experimental Biology, 31(4): 1326-1330, 1972.
E - gen. pap. - gen. disc. - review - tables - humans - chromosome damage - teratogenicity - intent. use - female consumpt. - male consumpt. - abort. rate - congenit. defects - premature birth - confound. agent. - hypothesis B-2681.

There have been few toxicological studies undertaken with the psychedelic drugs which are being taken by increasing numbers of young adults. There is also the difficulty that in most cases the composition and the purity of these drugs are not known. In addition, chromosome damaging substances and teratogens may not show any detrimental effect for generations. The author defines and differentiates the terms "genetic damage" and "teratogenic". He reviews the literature dealing with these two terms and reports the results of his investigation. Major structural anomalies were found in ten percent of the live births of children whose parents had used LSD before and/or during pregnancy. There was also a 42 percent incidence of spontaneous abortion. The conditions of these parents' living which may have been influential in the findings are listed. The article is concluded with a chemical discussion into the possible mechanisms behind the genetically detrimental effects of LSD.

36. Bick, Y. A. E.
COMPARISON OF THE EFFECTS OF LSD, HELIOTRINE AND X-IRRADIATION ON CHROMOSOME BREAKAGE, AND THE EFFECTS OF LSD ON THE RATE OF CELL DIVISION.
Nature, 226(5251): 1165-1167, 1970.
E - res. pap. - in vitro - tables - mammals - chromosome damage - exper. admin. - single dose - dose/response - chrom. aberr. - chrom. analysis, peripheral B-2682.

Reference to conflicting reports on the effects of LSD is given and new experiments are described. Chromatid and isochromatid deletions increased with doses of LSD (0. 4 to 6. 64 μg. /ml.) when added to leucocyte cultures of the rat kangaroo. The response was linear when concentration was plotted against total chromosome breakage. Due to the critical stage of cell growth at which LSD affects chromosomes, damage in LSD users cannot be estimated from peripheral leucocytes. Heliotrine, a hepatotoxin, and a reported chemical mutagen, produced the same order of damage as LSD. 100 R of radiation at 25 R per minute produced damage comparable to that of 4. 2 μg. /ml. of LSD. LSD inhibited mitosis,

but cells gradually overcame the inhibition. Explanations for this, differences in LSD metabolism, and application of these results to humans are discussed.

37. Blaine, J. D.
INCULPATION OF LSD CHALLENGED.
New England Journal of Medicine, 283(22): 1231, 1970.
E - lett. ed. - gen. disc. - humans - teratogenicity - oral admin. - congenit. defects - no effect - confound. agent. B-2683.

A report title "Bizarre deformities in offspring of user of lysergic acid diethylamide" is criticized on the basis of its unsubstantiated implications. LSD, used once at about the time of conception, was blamed and the high doses of estrogen and medroxyprogesterone acetate were not considered. Chromosome studies of the parents were not done. Conditions, such as malnutrition, which may contribute to congenital abnormalities were not discussed. Guidelines for proper study of teratogenesis are discussed. References to conflicting results of animal studies on the teratogenic potential of LSD are cited. A distinction is made between teratogenic and cytogenic effects. Caution is urged in reporting human cases linking birth defects with parental LSD usage until more definitive studies are performed on animal and clinical levels.

38. Blanc, W. A., Mattison, D. R., Kane, R., and Chauhan, P.
L. S. D., INTRAUTERINE AMPUTATIONS, AND AMNIOTIC - BAND SYNDROME.
Lancet, 2(7716): 158-159, 1971.
E - lett. ed. - gen. disc. - humans - teratogenicity - congenit. defects - placent. funct. - hypothesis B-2684.

The author reviews the congenital deformities of six infants born to mothers who had used LSD. The malformations in three of these infants were quite similar to those found with the amniotic-band syndrome. This syndrome is associated with the early rupture or separation of the membranes of the placenta. It is recommended that the placenta and fetal membranes be examined for ruptures in further cases of deformities associated with LSD ingestion.

39. Bloom, A. D.
INDUCED CHROMOSOMAL ABERRATIONS: BIOLOGICAL AND CLINICAL SIGNIFICANCE.
Journal of Pediatrics, 81(1): 1-8, 1972.
E - gen. pap. - sec. disc. - humans - chromosome damage -

chrom. aberr. - no effect B-2685.

The author discusses how somatic cell aberrations might arise and what their effect might be. It has been found that in populations with increased levels of induced aberrations, there is an increased risk of developing a malignant disease. A review of some of the studies with LSD is given to show the confusion that exists due to the lack of a uniform set of criteria in this area of investigation. The in vivo studies seem to suggest that some contaminants in illicit drugs or some social or physical condition of addicts cause chromosome aberrations. Pure LSD does not seem to cause any. An isochromatid break is a double break resulting from either one or two "hits". The criteria of break rate per cell is of little use with this type of break which appears often in LSD studies.

40. Bogdanoff, B., Rorke, L. B., Yanoff, M., and Warren, W. S.
BRAIN AND EYE ABNORMALITIES. POSSIBLE SEQUELAE TO PRENATAL USE OF MULTIPLE DRUGS INCLUDING LSD.
American Journal of Diseases of Children, 123: 145-148, 1972.
E - gen. pap. - case rep. - humans - female - teratogenicity - intent. use - extended use - female consumpt. - congenit. defects - death - autop. - birth, full term - chrom. analysis - lab. test.
B-2686.

A report is presented of a female infant born to a 19 year old mother who had smoked marijuana and had used LSD during pregnancy. The child suffered multiple malformations of the cerebrum and the cerebellum, and aqueductal stenosis and ocular abnormalities were also present. Routine laboratory studies, X-rays of the long bones, and chromosome analysis were normal. The child died at 13 months of age. The autopsy showed the dura adherent to the inner table of the skull and dense fibrous adhesions bound portions of the brain to the dura. The tentorium was incompletely developed and the optic nerves were atrophic. The ocular anomalies appeared to be of a developmental type. Comparisons are made between the abnormalities found in this case and those in 18 infants, reported in nine other papers, whose mothers had used LSD during pregnancy. Findings from animal studies are also mentioned.

41. Borgen, L. A., and Davis, W. M.
EFFECTS OF CHRONIC Δ-9-TETRAHYDROCANNABINOL ON PREGNANCY IN THE RAT.
Pharmacologist, 12: 259, 1970.
E - abst. - in vivo - rats - teratogenicity - exper. admin. - s. c.

admin. - extended use - female consumpt. - congenit. defects - fetal maldevel. - litter - no effect - birth, full term B-2687.

Synthetic Δ-9-tetrahydrocannabinol was subcutaneously administered to female rats daily on day 1 through 20 of gestation in doses ranging from .01 to 200 mg./kg. Effects on the females are listed. As for the offspring, frank teratogenesis and generalized stunting did not take place. Litter size decreased at the higher doses but the offspring showed normal growth and did not differ in their spontaneous or d-amphetamine stimulated activity.

42. Borgen, L. A., Davis, W. M., and Page, H. B.
EFFECTS OF SYNTHETIC Δ-9-TETRAHYDROCANNABINOL ON PREGNANCY AND OFFSPRING IN THE RAT.
Toxicology and Applied Pharmacology, 20: 480-486, 1971.
E - res. pap. - in vivo - tables - rats - teratogenicity - exper. admin. - s. c. admin. - extended use - female consumpt. - congenit. defects - fetal maldevel. - litter - no effect - birth, pre term. - birth, full term B-2688.

Synthetic Δ-9-tetrahydrocannabinol was subcutaneously administered to female rats daily on day 1 through 20 of gestation in doses ranging from .01 to 200 mg./kg. A number of females were sacrificed on the 21st day while the rest were allowed to deliver without disturbance. There was no significant incidence of gross malformations in the offspring. There was no increase in the number of stillborn young and no loss of entire litters. Litter size was reduced for the females receiving 100 mg./kg. of the drug. Many females in the higher dose groups had longer than normal pregnancies and those treated with doses greater than 50 mg./kg. lost a greater portion of their young postnatally. The body weight of the females treated with more than 10 mg./kg. was reduced during gestation.

43. Brady, A. H., Brady, E. M., and Boucek, F. C.
OPTICAL ACTIVITY OF LSD-DNA MIXTURES.
Nature, 232(5307): 189-190, 1971.
E - res. pap. - in vitro - mammals - chromosome damage - exper. admin. - chrom. aberr. - no effect B-2689.

There is some support for the belief that the intercalation of LSD in DNA is the cause of chromosome damage and abnormalities in human offspring. The author's work fails to show that LSD has any effect on DNA conformation. Circular dichroism of DNA in the presence of d-LSD was studied and significant changes were found.

The d-LSD-DNA spectra was just the combination of the individual d-LSD and DNA spectra. LSD had little effect on the optical activity of DNA which gives support to the stand that LSD does not have any effect on DNA.

44. Brazelton, T. B.
EFFECT OF PRENATAL DRUGS ON THE BEHAVIOR OF THE NEONATE.
American Journal of Psychiatry, 126(9): 1261-1266, 1970.
E - gen. pap. - sec. disc. - humans - chromosome damage - teratogenicity - intent. use - chrom. aberr. - congenit. defects - no effect B-2690.

The author discusses the effect which prenatal drugs have on the neonate and his behavior. The point is made that it is just as important in determining the outcome of the mother-infant interaction, what the baby is like as is the mother's personality structure. There is evidence that maternal ingestion of LSD results in persistent chromosome defects in the offspring which tend to repair incompletely. What congenital defects might arise in the next generation offspring? Both chromosome damage and abnormalities in fetuses have been shown. The stage of pregnancy at which LSD is taken is the most critical aspect of its use. The author goes on to discuss dietary inadequacy, sex hormone treatment, tranquilizers, and premedications and their effect on the infant and his behavior.

45. Bro-Rasmussen, F., Jensen, B., and Sørensen, A. H.
"SPONTANEOUS" AMPUTATIONS.
Lancet, 1: 907-908, 1972.
E - lett. ed. - gen. disc. - humans - mice - teratogenicity - exper. admin. - intent. use - female consumpt. - congenit. defects - placent. funct. - no effect B-2691.

From their studies with LSD and fluorodeoxyuridine, the authors did not find that congenital abnormalities connected with spontaneous amputations were due to amniotic bands caused by the rupture of the amnion during pregnancy. In analyzing 148 pregnancies after the ingestion of LSD, they found an increased risk of spontaneous abortion in mothers who had ingested LSD but no significantly increased risk of malformations in the infants. Fluorodeoxyuridine caused amputations and deformities in mouse fetuses but stereomicroscopic study did not reveal placental or amniotic membrane abnormalities, nor amputated fetal parts in the amniotic fluid. It is concluded that spontaneous amputations may be induced by terato-

genic agents through a primary vascular injury but their genesis is in doubt.

46. Browning, L. S.
LYSERGIC ACID DIETHYLAMIDE: MUTAGENIC EFFECTS IN DROSOPHILA.
Science, 161(3845): 1022-1023, 1968.
E - res. pap. - in vivo - fruit flies - chromosome damage - exper. admin. - i. p. admin. - single dose - male consumpt. - chrom. aberr. - spermatogen. effect B-2692.

An experiment was undertaken which showed a significant increase in recessive lethal mutations in Drosophila males after an intraperitoneal injection of LSD. Only the mature sperm were appreciably affected and only when a very high dose (4000 µg./g.) was used. Partial sterility also occurred. The significance should not be discounted on the basis of the dose however, because many other chemicals are nonmutagenic at toxic levels. Reference to conflicting reports on the effects of LSD on chromosomes in vitro and in vivo is made.

47. Buckman, J.
SOCIAL AND MEDICAL ASPECTS OF ILLICIT USE OF LSD.
International Journal of Social Psychiatry, 17: 163-176, 1971.
E - gen. pap. - review - humans - mammals - chromosome damage - teratogenicity - chrom. aberr. - congenit. defects - no effect B-2693.

The author reviews the literature on the many different aspects of the therapeutic and illicit use of LSD. The questions examined in this paper are: what is the nature and extent of illicit LSD use, who are the ones misusing it, what is the nature of the LSD experience, what are the dangers to the individual or to the society, and what is the nature of society's reaction. Reference is made to many of the studies undertaken in connection with chromosome damage. This review clearly shows the contradictory results that have been found and the subsequent controversy. LSD may be responsible for a higher rate of resorptions, abortions, and malformations of the fetuses of small animals. Animal studies and case reports of deformed human infants are presented.

48. Budini, R., Letizia Vannini, M., and Tubertini, O.
RNA IN PLANARIANS (DUGESIA LUGUBRIS) TREATED WITH LSD.
Experientia, 29(3): 274-275, 1973.
E - res. pap. - in vivo - mammals - chromosome damage - exper. admin. - extended use B-2694.

An in vivo experiment was undertaken with 600 planarian Dugesia lugubris. The LSD treated specimens were kept in a spring water solution of LSD-tartrate for eight days. To obtain some radioactivity, tritiated uridine was added on the last day. The planarians were then cut in two pieces by a cutting plane anterior to the pharynx. The sections were analyzed for total phosphorus and for the radioactivity of the RNA. It was found that LSD increased the concentration of RNA in the cephalic sections containing a large number of nerve cells but that in the retrocephalic sections, the amount of RNA was the same as was found in the control planarians. There was also a significantly greater amount of radioactivity in the cephalic sections than in the retrocephalic sections. The mechanism for these effects which LSD has on the cephalic sections of the planarians is in doubt.

49. Carakushansky, G., Neu, R. L., and Gardner, L. I.
LYSERGIDE AND CANNABIS AS POSSIBLE TERATOGENS IN MAN.
Lancet, 1: 150-151, 1969.
E - lett. ed. - case rep. - female - teratogenicity - intent. use - female consumpt. - congenit. defects - premature birth - birth, full term - chrom. analysis, peripheral B-1236.

A report is given of a first infant born to a mother who had been exposed to LSD and cannabis during pregnancy. The girl was born prematurely and suffered bone deformities in her hands and feet. No chromosome aberrations were found in the peripheral leucocytes of the child. Reference to reports of similar deformities is made.

50. Carter, C. H., Carpenter, D. G., and Connolly, J. M.
LYSERGIC ACID DIETHYLAMIDE AND CHROMOSOME DAMAGE. ITS CONTROVERSY.
Journal of the Florida Medical Association, 59(2): 29-31, 1972.
E - gen. pap. - gen. disc. - review - humans - chromosome damage - teratogenicity - intent. use - oral admin. - female consumpt. - male consumpt. - chrom. aberr. - chrom. analysis, peripheral - confound. agent. B-2695.

The author reviews the literature concerning the effect of LSD in vitro and in vivo on chromosomes. The difficulties inherent in the work done in this area are expressed. A large number of widely used drugs and physical agents have been implicated in causing chromosome damage. This influence can not be excluded from either the control or the study subjects. The little amount of knowledge about the restitution of chromosome breaks is also an impediment. Fifteen patients were found to have severe chromosome aberrations of the 20 studied between the ages of 14 and 22 years, who had used LSD along with other drugs. The other five had definite but lighter damage. Three children born of parents who had used LSD were found to have a slight macrocephaly and moderate atonia in the one, a severe exencephaly in the second, and a midfacial cleft in the third. Valuable information must be obtained from careful study and documentation of the generations of offspring of the many LSD exposed persons.

51. Chibon, P., and Bélanger-Barbeau, M.
EMBRYOLOGIE EXPÉRIMENTALE. -EFFECTS DU LSD SUR LE DÉVELOPPEMENT EMBRYONNAIRE ET LES CHROMOSOMES DE L'AMPHIBIEN URODÈLE PLEURODELES WALTLII MICHAH. [Embryological experimentation. -The effects of LSD on the development of embryos and the chromosomes of the amphibian urodele Pleurodeles waltlii Michah.]
Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences. Serie D. Sciences Naturelles, 274(2): 280-283, 1972.
F - res. pap. - in vivo - amphibians - chromosome damage - teratogenicity - exper. admin. - single dose - dose/response - stage of devel. - abort. rate - chrom. aberr. - death - embryo. maldevel.
B-2696.

There still exists a great controversy regarding the teratogenic properties of radiation, viruses, and chemical agents. Due to the current extent of the illicit use of LSD, the authors felt that it was important to study the possible teratogenic or mutagenic properties which this drug might have. They used the newt Pleurodeles waltlii Michah and examined the effects of various doses of LSD at various stages of its embryonic development. They also proposed the study of the future progeny of these specimens treated with LSD. The drug was added in varying concentrations (ranging between 0.01 and 2.5 mg./ml.) to a breeding solution. The embryos were then placed in this solution for 3 hours, after which they were transferred to a second breeding solution which was renewed every day. This solution was the same as was used for the control group. The results showed that the older the embryos were, the better they resisted the toxic action of the substance. Although the gravity of the effects decreased with the weaker doses, as did the mortality

rate, the percentage of abnormalities among the survivors remained high. The authors conclude that LSD simultaneously affected the embryonic development as well as the chromosomes, and that these two effects are evidently related.

52. Cohen, M. M., Marinello, M. J., and Back, N.
CHROMOSOMAL DAMAGE IN HUMAN LEUKOCYTES INDUCED BY LYSERGIC ACID DIETHYLAMIDE.
Science, 155(3768): 1417-1419, 1967.
E - res. pap. - in vivo - in vitro - humans - chromosome damage - exper. admin. - therapeut. use - single dose - extended use - male consumpt. - dose/response - chrom. aberr. - chrom. analysis, peripheral B-2697.

LSD was added to cultures of peripheral leukocytes from two people and induced a significant number of chromosomal breaks and rearrangements. The techniques and scoring used are described. A dose-response table and pictures are also provided. At most concentrations, the greatest damage was induced by the 24- and 48-hour exposures. In addition, the leukocytes of a paranoid schizophrenic were examined eight months after his 15th treatment with LSD. The breakage rate was 12 percent compared to the normal 3.7 percent. There was one quadriradial formation between two number 1 chromosomes. Reports of other conditions and drugs which cause similar changes are discussed. LSD may act by causing permanent damage to stem cells that give rise to leukocytes, or more likely, by causing damage to long-lived lymphocytes in the G_1 period. Reference to reviews of induced breakage of chromosomes is given.

53. Cohen, M. M., Hirschhorn, K., and Frosch, W. A.
IN VIVO AND IN VITRO CHROMOSOMAL DAMAGE INDUCED BY LSD-25.
New England Journal of Medicine, 277(20): 1043-1049, 1967.
E - res. pap. - in vivo - in vitro - humans - chromosome damage - exper. admin. - intent. use - chrom. aberr. - chrom. analysis, peripheral B-2698.

Chromosomes in the peripheral leucocytes of six healthy non-drug users were studied in vitro. In addition, the chromosomes of 22 persons who had ingested LSD or who had been exposed to it in utero, six patients who were receiving other drugs, and 14 drug free controls were examined. Graphs, diagrams, and tables detail the results. In vitro, most abnormalities, two times as many as in the controls, were chromatid and isochromatid breaks, with a few

chromatid exchanges and dicentric chromosomes. There were no ring chromosomes and there occurred a marked reduction in mitosis. In the LSD users, the mean incidence of damage was three times that of the controls and similar to the in vitro pattern. No structural rearrangements were seen in the controls. Two children exposed in utero early in pregnancy showed more damage than the two exposed to LSD late in pregnancy. Patients receiving chlorpromazine showed a marked increase in chromosome breaks. Eight references are given to discussions on the mechanism of breakage and eight others deal with spontaneous aberrations in three autosomal recessive diseases. The possibility of congenital defects in humans, as have been demonstrated in animals, is discussed.

54. Cohen, M. M.
LSD AND CHROMOSOMES.
Science Journal, 4(9): 76-79, 1968.
E - gen. pap. - gen. disc. - humans - chromosome damage - exper. admin. - chrom. aberr. - carcinogen. effect - no effect - chrom. analysis, peripheral - drug action B-0724.

The effects of hallucinogens, a subgroup of psychotropic drugs, are described. The synthesis of LSD in 1938, its chemistry, psychological and physiological effects, and those of other drugs are discussed and compared. In cultures of leucocytes of 18 LSD users, and of 6 non drug users in which LSD was added in vitro, chromatid and isochromatid breaks, dicentric chromosomes, and terminal deletions were found. Significantly fewer changes were found in 14 non drug users. Mitosis was suppressed by LSD in vitro. Eight of 12 children whose mothers took LSD during pregnancy showed a two-fold increase in damage compared to the normal. Chromosomal anomalies occurred in 75 to 80 percent of the 220 LSD users reported in the U. S. A. Radiation, viruses, and other chemicals can cause similar changes and have been associated with cancer. This may be another effect of LSD. Other hazards include genetic defects, prolonged behavioral derangement, or delayed psychotic episodes. Therapeutic use is not advised.

55. Cohen, M.M., Hirschhorn, K., and Frosch, W. A.
LSD AND CHROMOSOMES.
New England Journal of Medicine, 278(4): 222-223, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - exper. admin. - intent. use - chrom. aberr. - no effect - chrom. analysis, peripheral B-2699.

Responding to a critique of their work, the authors explain that, in vitro, the lack of increased chromosome damage with higher doses of, or length of exposure to LSD could possibly be due to the fact that LSD suppresses mitosis and causes cellular destruction. There could be an effect, above which no cytogenetic analysis is possible. It is pointed out, again, the difficulty with in vitro to in vivo extrapolations concerning the doses of the drug used. They do note however, that the concentrations tested in vitro included the estimated in vivo doses. Structural rearrangements were observed in only LSD users. These are potentially the most dangerous type of aberrations.

56. Cohen, M. M., and Mukherjee, A. B.
MEIOTIC CHROMOSOME DAMAGE INDUCED BY LSD-25.
Nature, 219(5158): 1072-1074, 1968.
E - res. pap. - in vivo - mice - chromosome damage - exper. admin. - i.p. admin. - single dose - chrom. aberr. - spermatogen. effect - chrom. analysis, bone mar. B-2700.

Reference is made to seven in vitro and in vivo studies on the chromosome breakage potential of LSD to the cells of humans and to one study on mice which compared the effects of LSD on various tissues. Chromosomal preparations were made from femoral bone marrow and testicular tissue of 13 mice. There was a ten-fold increase in anomalies in the ten injected mice, which received 25 μg./kg., intraperitoneally, compared to the three controls. Bone marrow metaphases were more vulnerable to chromosome damage than the somatic or meiotic cells. Mice were killed one to 21 days after injection. The results are itemized and the types of anomalies are illustrated. They included chromatid and isochromatid breaks, metacentric and submetacentric chromosomes. Cells tended to return to normal but after three weeks, there were still seven times as many abnormalities than normal in the bone marrow cells. Genetic implications are discussed. Reduced fertility, congenital abnormalities, and foetal wastage may occur.

57. Cohen, M. M., Hirschhorn, K., and Frosch, W. A.
THE CYTOGENETIC EFFECT OF EXPOSURE TO LSD IN UTERO.
Pediatric Research, 2(4): 296-297, 1968.
E - abst. - in vivo - humans - chromosome damage - intent. use - female consumpt. - chrom. aberr. - no effect - chrom. analysis B-2601.

Chromosomes were examined from 12 infants exposed to LSD in

utero, their mothers and seven other adult users as well as a corresponding non drug using control group. The mean chromosome breakage rate in the controls was 1.26 percent compared to 8.72 percent in the test group. Results were similar in the children, alone. Structural rearrangements (six dicentric and two quadriradial) were seen in the exposed group but not in the control group. There were no obvious birth defects. It is noted that LSD had induced chromosomal aberrations in vitro and in vivo. This effect could result in neoplasia in the user, teratogenic effect on the fetus, and genetic effect through chromosomal aberrations in gametes.

58. Cohen, M. M., Hirschhorn, K., Verbo, S., Frosch, W. A., and Groeschel, M. M.
THE EFFECT OF LSD-25 ON THE CHROMOSOMES OF CHILDREN EXPOSED IN UTERO.
Pediatric Research, 2(6): 486-492, 1968.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - female consumpt. - chrom. aberr. - spermatogen. effect - chrom. analysis, peripheral B-2702.

The chromosomes were examined in the peripheral leucocytes of nine children exposed to LSD in utero, four whose parents had used it before pregnancy, their mothers and six other adults who had taken it along with 15 persons in a control group. The results are tabulated. There were significantly increased frequencies of chromosomal damage in all those exposed, but less in the children not exposed in utero. The two children with the most damage were also exposed to other hallucinogens, including psilocybin. Six dicentric chromosomes and two quadriradial formations were seen. None were found in the controls. All the subjects seemed to be healthy and there were no birth defects. Abortion or birth defects may occur if LSD is ingested at a critical time in gestation. A mutagenic effect of LSD on spermatogonial cells is discussed, in view of its effect on somatic cells. In evaluating conflicting reports on LSD, the effects of impurities, use of other drugs, and infection are mentioned. Reported association between cytogenetic imbalance and neoplasia is discussed.

59. Cohen, M. M.
THE INTERACTION OF VARIOUS DRUGS WITH HUMAN CHROMOSOMES.
Canadian Journal of Genetics and Cytology, 11(1): 1-24, 1969.
E - gen. pap. - review - humans - mice - chromosome damage - exper. admin. - intent. use - oral admin. - dose/response -

chrom. aberr. - no effect - chrom. analysis, peripheral - confound. agent. B-2703.

The author reviews the literature on the effects of streptonigrin, mitomycin C, and LSD on human chromosomes. Most of the findings which have implicated LSD as causing chromosome damage have been countered with negative results utilizing almost the same test systems. It has been found in vitro that the suppression of mitosis is enhanced the longer the chromosomes are exposed to LSD. The chromosome breaks which have been found do not fall into a set pattern. However, it does appear that the centromeric regions, as well as the heterochromatic secondary constrictions of many chromosomes, are vulnerable to LSD breakage. It has been found that structural rearrangements such as biarmed chromosomes have been observed in spermatogonial metaphase of mice. This is a highly significant piece of additional information. Many LSD users have shown chromosome damage but others have not. The response may vary on an individual basis like that of many other drugs. The effects which these people's social and physical conditions may have on this type of investigation must also be considered.

60. Cohen, M. M.
"GENETIC" DISTURBANCES ASSOCIATED WITH LSD.
In: Hicks, R. E., and Fink, P. J., eds. Psychedelic Drugs.
New York: Grune and Stratton, pp. 66-75, 1969.
E - book - gen. disc. - review - fruit flies - humans - mammals - chromosome damage - exper. admin. - intent. use - chrom. aberr. - no effect - chrom. analysis B-2704.

The author discusses the research which his group of workers has carried out on the effects of LSD on chromosomes. The results of other experiments are included to provide supporting and conflicting evidence for his findings. The different experimental approaches to the study of chromosomes are given along with the classification and the scoring of chromosomal damage. It was found from in vitro experiments that LSD causes suppression of mitosis. In addition, it was found that the frequency of chromosomal abnormalities was two to four times higher in the experimental cultures than in the control cultures. Abnormalities consisted mainly of chromatid and isochromatid breaks which seemed to be incurred in a nonuniform pattern. In vivo studies supported the initial in vitro findings. In one study, chromosomal abnormalities in LSD users ranged from the control levels of 5 percent to in excess of 25 percent. The types of breaks were similar to those found in in vitro studies, however, dicentric chromosomes and exchange figures

were also observed. Similar results were found in children exposed to LSD in utero. Meiotic chromosomal abnormalities were found in male rodents injected with LSD. Support has been given from other in vivo experiments. Of an approximate total of 250 LSD users, increased chromosomal breakage frequencies have been found in 65 to 85 percent. It was also realized that the individual susceptibility to this effect of the drug varies greatly. The confounding aspects of this type of research with LSD and the potential danger of these chromosomal damaging effects of LSD are discussed.

61. Corey, M. J., Andrews, J. C., McLeod, M. J., MacLean, J. R., and Wilby, W. E.
CHROMOSOME STUDIES ON PATIENTS (IN VIVO) AND CELLS (IN VITRO) TREATED WITH LYSERGIC ACID DIETHYLAMIDE.
New England Journal of Medicine, 282: 939-943, 1970.
E - res. pap. - in vivo - in vitro - humans - chromosome damage - exper. admin. - oral admin. - single dose - chrom. aberr. - chrom. analysis, peripheral B-2705.

Ten patients were given a therapeutic dose (200 to 600 μg., orally) of LSD. Chromosomes in the blood samples taken immediately before and 24 hours after did not differ in the number of breaks. In addition, patients who had been on long term therapy with LSD, mescaline, and other drugs were also tested and no significant aberrations were found. In vitro tests showed a significant increase in single and total breaks, but not in double break aberrations. Differences in reported effects in vivo seem to depend on whether the experimental group ingested illicit or pure LSD. Therapeutic use of pure LSD appears harmless to chromosomes but the cause of aberrations in users of illicit LSD should be sought.

62. Court Brown, W. M.
IS LYSERGIDE A TERATOGEN?
Lancet, 2(7526): 1154, 1967.
E - lett. ed. - gen. disc. - humans - chromosome damage - intent. use - female consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2706.

The importance of thorough reporting of work undertaken in this area is stressed. The time in culture of the chromosomes and the nature of any aberrations must be given. The number of cells analyzed and the degree to which they were studied must be given.

63. Denson, R.
EFFECTS OF LSD ON CHROMOSOMES.
Canadian Medical Association Journal, 98: 609, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - chrom. aberr. - no effect - chrom. analysis, peripheral B-2707.

Authors' bias, towards finding LSD a teratogen in chromosome studies in humans, is noted in a letter suggesting a misleading editorial assessment (Canad. Med. Ass. J., 98: 221, 1968) of a report by Cohen et al. Attention is drawn to the group in the study who had viral infections or who took other drugs, principally chlorpromazine, and whose rate of chromosome breaks was not significantly lower than that of the LSD users. It is asked why LSD was singled out as harmful and not chlorpromazine or other drugs. Drug addicts who used LSD were compared with normal controls, instead of other addicts not using LSD. Thus, the chromosome damage cannot, solely, be attributed to LSD. The few doses used in therapy, compared to the large number by addicts make criticism of therapeutic use invalid, if based only on the possible ill effects in addicts.

64. DiPaolo, J. A.
LSD: EFFECTS ON OFFSPRING.
Science, 158: 522, 1967.
E - lett. ed. - gen. disc. - rats - teratogenicity - exper. admin. - s. c. admin. - single dose - female consumpt. - abort. rate - congenit. defects - no effect B-2708.

Criticism of two experiments concerning the teratogenic effects of LSD is offered in a letter. It is suggested that the conclusions about LSD effects on offspring were unwarranted in one, on the basis of one subcutaneous injection in rats prior to conception. Oral administration, doses during different periods of gestation, and interruption of the pregnancy to provide valid conclusions about missing embryos, are suggested. In the second study, extrapolation, from cultured human lymphocytes from an in vitro to an in vivo system, is thought just as dangerous as extrapolation from one species to another. The potential hazard of LSD is recognized, but better designed studies are urged.

65. DiPaolo, J. A., Givelber, H. M., and Erwin, H.
EVALUATION OF TERATOGENICITY OF LYSERGIC ACID DIETHYLAMIDE.
Nature, 220: 490-491, 1968.
E - res. pap. - in vivo - in vitro - mice - mammals - chromo-

some damage - teratogenicity - exper. admin. - i. p. admin. - single dose - extended use - female consumpt. - chrom. aberr. - congenit. defects - no effect - birth, pre term. - chrom. analysis B-2709.

Fourteen Syrian hamsters were injected intraperitoneally with 10, 100, or 300 μg. of LSD on days 6, 7, or 8 of gestation. Repeated doses of 100 μg. were given to one on days 7, 8, and 9. Pregnancies were terminated on the 14th day. There was no difference from the controls with respect to weight changes or to the number of resorbed fetuses. There was one case of microphthalmia. In vitro tests on cells and chromosomes of hamster embryos were negative. Mice were given multiple intraperitoneal injections totalling 5 to 30 μg. of LSD on the 7th day of gestation, the critical stage of development. Of 79 foetuses from the 14 treated females, 15 foetuses from six litters had a harelip, cleft palate, or micrognathia. Of 65 foetuses from ten litters of the control group, two foetuses (from the same litter) had defects similar to those in the LSD group. Thus, LSD was not proven to be teratogenic to Syrian hamsters or to the mice used. It is suggested that the relatively low number of defects obtained with doses ranging from 25 to 1,000 times the average single dose taken by humans, may reflect potentiation of individual threshold differences for specific malformations. Reports are cited on threshold differences in response to other agents.

66. Dishotsky, N. I., Loughman, W. D., Mogar, R. E., and Lipscomb, W. R.
LSD AND GENETIC DAMAGE.
Science, 172(3982): 431-440, 1971.
E - gen. pap. - review - tables - fruit flies - humans - mice - rats - chromosome damage - teratogenicity - exper. admin. - intent. use - female consumpt. - chrom. aberr. - congenit. defects - carcinogen. effect - no effect - confound. agent. B-2710.

An analysis of the literature shows that LSD, ingested in moderate doses, does not damage chromosomes in vivo, does not cause detectable genetic damage, and is not a teratogen or carcinogen in man. The absence of excretory and detoxifying systems in vitro, and conflicting reports, cast doubt on the relevance of in vitro results. Only 18 of 126 (14 percent) subjects exposed to pure LSD showed more chromosomal aberrations than did the controls, compared to 90 of 184 (49 percent) of those taking illicit LSD. It is suggested that the role of other drugs (many listed), impurities, hepatitis and other viral infections, and malnutrition need to be evaluated. No cause-and-effect relation, and no increase in the

incidence of neoplasia has been reported in LSD users. Experiments on Drosophila suggest that LSD is a weak mutagen, effective only in very high doses. A review of 15 rodent studies indicated a wide range of individual, strain, and species susceptibility to LSD. Applicability to man is doubtful. In studies of human pregnancies, those exposed to LSD had a higher than normal rate of spontaneous abortion. There were six cases of malformation but these could be spontaneous congenital defects. There is no reported instance of a malformed child born to a woman who had ingested pure LSD.

67. Dorrance, D., Janiger, O., and Teplitz, R. L.
IN VIVO EFFECTS OF ILLICIT HALLUCINOGENS ON HUMAN LYMPHOCYTE CHROMOSOMES.
Journal of the American Medical Association, 212(9): 1488-1491, 1970.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - chrom. aberr. - no effect - chrom. analysis, peripheral B-1424.

An in vivo experiment was undertaken with 14 subjects who had been exposed to LSD and nine subjects who had been exposed to marijuana along with a group of age-matched controls. Peripheral venous blood was drawn from each subject. The methodology used to prepare the cultures is given. The LSD group showed from one to 175 doses taken. The time of the last exposure ranged from 1 1/2 hours to three months before sampling. Eight breaks in 1,284 metaphase spreads (0.76 percent) were found. The only types of abnormalities found were chromatid breaks and fragments. The time of the last dose of marijuana ranged from 12 hours to one month prior to sampling. Seven breaks in 816 metaphase spreads (0.86 percent) were found. The types of breaks were the same as in the LSD group. Eight breaks in 1,018 metaphase spreads (0.79 percent) were found in the control group. All the cells were grown in medium unenriched with nucleotide precursors. The negative results of this study rule out medium deficiency as contributing toward positive effects. The fact that the last doses of LSD and marijuana were taken, in some cases, shortly before sampling rules this factor out as a cause for the conflicting results found in other studies.

68. Dumars, K. W., Jr.
PARENTAL DRUG USAGE: EFFECT UPON CHROMOSOMES OF PROGENY.
Pediatrics, 47(6): 1037-1041, 1971.

E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - female consumpt. - male consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2711.

Chromosome studies were performed on the parents and the newborn in 47 cases in which it was determined that LSD had been taken during pregnancy. The amount of LSD that had been taken by the different parents could not be determined accurately, and most parents had used many additional, illicit drugs besides LSD. It was found that chromosome breakage occurred in less than 1.5 percent of the chromosome karyotypes of both the experimental and the control group. No structural rearrangements were found and no significant difference was found. The infants born to illicit drug users showed no increase in chromosome breakage or structural rearrangement.

69. Egozcue, J., Irwin, S., and Maruffo, C. A.
CHROMOSOMAL DAMAGE IN LSD USERS.
Journal of the American Medical Association, 204(3): 214-218, 1968.

E - res. pap. - in vivo - humans - chromosome damage - intent. use - extended use - female consumpt. - male consumpt. - chrom. aberr. - carcinogen. effect - chrom. analysis, peripheral B-2712.

Chromosomes in the leukocytes of 46 adult LSD users, and four children exposed in utero, had a mean of 18.2 percent of breakage compared to 9.0 percent for 14 drug free controls. Most of the users had also taken marijuana and other drugs. The abnormalities were largely chromatid and isochromatid, but 16 dicentric chromosomes and ten exchange figures were seen (pictures are given). There was an excess of breaks in chromosomes one and two, and a paucity in groups E and F, in the 30 subjects in which breaks were assigned to specific chromosomes. There was no depression of mitosis, as has been found by others in vitro, and no correlation between the number of breaks and the total dose of LSD. LSD may cause neoplasia as is found in other syndromes with a similar chromosome picture. The anomalies seen can also be produced by carcinogenic viruses and radiation. Reference to reports on the relation to leukemia, congenital defects in rats, mice, hamsters, and one human is made. Morning glory seeds contain LSD and their effects on chromosomes are now being tested.

70. Egozcue, J., and Irwin, S.
EFFECT OF LSD-25 ON MITOTIC AND MEIOTIC CHROMOSOMES OF MICE AND MONKEYS.
Humangenetik, 8(2): 86-93, 1969.
E - res. pap. - in vivo - in vitro - mice - primates - chromosome damage - exper. admin. - i.p. admin. - oral admin. - single dose - extended use - female consumpt. - male consumpt. - chrom. aberr. - spermatogen. effect - chrom. analysis, peripheral - chrom. analysis, bone mar. B-2713.

In vitro and in vivo experiments were undertaken with mice and monkeys. The mice had one testis removed before injection to act as a control while the second was removed 24 hours after the injection of 10, 15, 30, 45, or 60 μg./kg. Additional administrations from two to ten (one per day) were also undertaken with the mice. The effect of LSD on meiosis was then determined. The mice were then killed to obtain bone marrow preparations. Blood samples of 12 male and female monkeys were cultured to determine if LSD causes chromosome breaks in the cultures of these animals. Four monkeys had LSD put into their stomachs by means of a catheter in doses of 5, 10, 20, or 40 μg./kg. A testicular biopsy was obtained before and after administration. Three of these monkeys continued to receive LSD at 10-day intervals. With the investigation of the bone marrow of the mice, the mean number of structural anomalies was similar between the chronic experimental (3.9 percent) and the control group (3.6 percent). In the acute experimental group, the incidence was higher at 5.3 percent. Since this picture was reversed in the spermatogonial metaphases, the authors feel these results are essentially negative. No significant differences were found in the meiotic chromosomes of the monkeys before and after chronic LSD treatment. However, there was a significant increase in chromosome breaks in both the in vitro and in vivo studies using the monkeys' blood. The mean breakage rate in the LSD-treated cultures was 29.4 percent versus 11.8 percent in the controls. LSD had little effect in the bone marrow or germ cells of mice or the germinal cells of the monkey. However, it does seem to act preferentially on the peripheral blood leukocytes of the monkeys.

71. Eller, J. L., and Morton, J. M.
BIZARRE DEFORMITIES IN OFFSPRING OF USER OF LYSERGIC ACID DIETHYLAMIDE.
New England Journal of Medicine, 283(8): 395-397, 1970.
E - gen. pap. - case rep. - humans - female - teratogenicity - intent. use - single dose - female consumpt. - stage of devel. - congenit. defects - death - autop. - lab. test B-2715.

Gross congenital defects in a white infant, born to a mother who had used LSD on one occassion close to the time of conception (and had taken medroxyprogesterone acetate), resembled spondylothoracic dysplasia. This group of anomalies (pictures are presented) has only been reported previously in six Puerta Rican infants (most from consanguineous marriages) with no history of LSD use. The girl had craniolacunia, radischisis, with urinary tract anomalies, and died 41 days after birth. Autopsy findings included a horseshoe kidney, single midline adrenal gland, Arnold-Chiari malformation with hydrocephalus, fusion of the frontal lobes of the brain, and bilateral interstitial pneumonia. The chromosomes were normal. Reference to other reports of mild deformities and chromosomal aberrations related to LSD is given. Etiology may involve the autosomal recessive mode of inheritance in some cases. The relation of LSD to these defects is unknown.

72. Eller, J. L.
LSD: WHAT INDEX OF SUSPICION?
New England Journal of Medicine, 284(3): 161, 1971.
E - lett. ed. - gen. disc. - humans - teratogenicity - congenit. defects - no effect B-2716.

The author points out that his previous report was not presented to prove a relationship between LSD and congenital defects in human newborns but to stimulate other reports of cases which might be similar. Both the impracticality and the impossibility of undertaking definitive clinical studies is expressed. More knowledge is being gained on this subject and the reporting of all cases and findings is one way of bearing more light onto this controversy.

73. Emerit, I., Roux, C., and Feingold, J.
LSD: NO CHROMOSOMAL BREAKAGE IN MOTHER AND EMBRYOS DURING RAT PREGNANCY.
Teratology, 6(1): 71-73, 1972.
E - res. pap. - in vivo - rats - chromosome damage - exper. admin. - i.p. admin. - extended use - female consumpt. - chrom. aberr. - no effect - birth, pre term. - chrom. analysis, bone mar. B-2717.

Nine pregnant rats were intraperitoneally injected with 500 µg./kg. per day of LSD from the 7th to the 13th day of pregnancy. The animals were killed two hours after the last dose and the bone marrow of both maternal femurs was used in the study of the chromosomes. A cell suspension was obtained of the 13-day embryos so that a direct examination of mitoses could be made with them. The

individual results using the bone marrow ranged from 3. 8 to 16 percent of mitoses with structural chromosome abnormalities. These consisted of gaps, breaks, and acentric fragments. The percentages are not higher than is normal without LSD. In the embryonic tissue, the frequency of mitoses with structural chromosome aberrations was lower in the treatment group than in the controls. From this, both negative cytogenetic and teratological results were obtained from this study.

74. Fabro, S., and Sieber, S. M.
IS LYSERGIDE A TERATOGEN?
Lancet, 1(7543): 639, 1968.
E - lett. ed. - in vivo - rabbits - teratogenicity - exper. admin. - oral admin. - extended use - female consumpt. - congenit. defects - embryocidal - no effect - birth, pre term. B-2718.

The embryotoxic activity of lysergide is compared with that of thalidomide in the New Zealand white rabbit. The drugs (LSD at 20 or 100 μg./kg., thalidomide at 150 mg./kg.) were given by stomach tube in an aqueous suspension, daily, at different intervals between days 4 and 12 of gestation. The females were killed on the 28th day. Thalidomide exerted its well known effects. In contrast, LSD treated does were not significantly different from the untreated controls in the average number of implantations, incidence of resorption, or the average weight of the offspring. No gross malformations were detected. Species differences in teratogenic activity are well known so that negative results with rabbits do not exclude LSD from being teratogenic in other species. References to the effects of LSD on the chromosomes in humans and to the teratogenic effects in animals and one human baby are cited.

75. Falek, A., Jordan, R. B., King, B. J., Arnold, P. J., and Skelton, W. D.
HUMAN CHROMOSOMES AND OPIATES.
Archives of General Psychiatry, 27: 511-515, 1972.
E - res. pap. - in vivo - in vitro - humans - chromosome damage - intent. use - female consumpt. - male consumpt. - chrom. aberr. - chrom. analysis, peripheral B-2719.

Two leukocyte cultures were prepared for each of 16 drug users who were involved in a methadone maintenance program. The addicts had taken most of the illicit drugs with the exception of LSD. The cultures were incubated for either 48 or 72 hours. The increased frequency of chromosome damage in the multiple drug patients was significant in the 72 hour culture. A total of 32 breaks

of 2,034 cells analyzed were found with the drug users compared to only 4 breaks of 1,499 cells analyzed with the control group. Along with the more common gaps and breaks, dicentric figures were found in six patients and one exchange figure was noted. In vitro studies were conducted with leukocytes obtained from the cord blood of newborn infants. Morphine, quinine, and methadone were examined separately in concentrations ranging from three times normal: quinine, .33 mg./ml.; morphine, .002 mg./ml.; methadone, .013 mg./ml.) through one twelfth normal concentration. Each was introduced at 24, 48, or 68 hours after culture initiation and incubation lasted for 72 hours. No significant increase in chromosome aberrations was found with any of these drugs.

76. Fitzgerald, P. H., and Dobson, J. R. E.
LYSERGIDE AND CHROMOSOMES.
Lancet, 1: 1036-1037, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - chrom. aberr. - no effect B-2720.

In this letter, the author expresses his concern that the widespread reporting of the unsubstantiated findings that LSD causes chromosomal damage might discourage the therapeutic use of the drug. Several studies have shown LSD to cause chromosomal damage. This has been taken as an indication that LSD is a mutagene, leukemogene, and a teratogene. It is not necessarily so. Agents are discussed which have some of these properties but not others. It cannot be assumed that because a substance has one of these properties that it must have the others. The author rejects the claim that LSD produces chromosome damage even weeks after its use. This misconception is based on the persistence of chromosomal damage in dormant small lymphocytes. Several commonly administered agents such as aspirin, ergometrine maleate, chlorpromazine, and irradiation are also known to cause serious genetic damage and far less is said about these agents.

77. Fitzgerald, P. H., and Dobson, J. R. E.
RADIOMIMETIC PROPERTIES OF LSD.
New England Journal of Medicine, 278: 1404, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - chrom. aberr. - no effect B-2721.

The author expresses his concern that the widespread reporting of the unsubstantiated findings that LSD causes chromosomal damage might discourage the responsible use of the drug. Several studies

have shown LSD to cause chromosomal damage. This has been taken as an indication that LSD is a mutagene, leukemogene, and teratogene, as well. It is not necessarily so. It cannot be assumed that because a substance has one of these properties that it must have the others. Several commonly administered agents such as aspirin and irradiation are known to cause even more serious genetic damage but far less is said about these agents.

78. Friedel, W.
LSD AND CHROMOSOMES.
Chicago Medical School Quarterly, 29(1-2): 9-23, 1970.
E - gen. pap. - review - tables - fruit flies - humans - mice - mammals - rabbits - rats - chromosome damage - teratogenicity - exper. admin. - intent. use - i. p. admin. - oral admin. - single dose - extended use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - carcinogen. effect - litter - no effect - chrom. analysis B-2722.

The author presents a review of the literature dealing with the chromosomal effects of LSD under the headings: In Vitro, In Vivo, In Animals, In Meiotic Chromosomes, In Utero (Exposed Children), and Significance. LSD does depress mitotic rates in relation to the length of exposure in human leukocyte cultures. Specific chromosomal aberrations are produced but the rate of damage is not dose-related. There is contradictory evidence from the in vivo studies. Only some of the researchers have found an increase in the chromosomal aberration rates of LSD users over non-users. Animal studies demonstrate that LSD, if administered early enough in pregnancy, can produce congenital malformations of the nervous system in mice and hamsters. The malformation rate is unrelated to the dose, however, a relationship does exist between the dose and litter size. Low doses of LSD cause transient abnormalities in meiotic chromosomes of rats. Higher doses cause chromosomal aberrations and are mutagenic in fruit flies. Some in utero studies with children indicate that high doses early in pregnancy produce more aberrations than lower doses later and may cause Ph-like chromosomes. The evidence that LSD has mutagenic, teratogenic, and carcinogenic potential is still unsubstantiated.

79. Fuchs, F., and Cederqvist, L. L.
RECENT ADVANCES IN ANTENATAL DIAGNOSIS BY AMNIOTIC FLUID ANALYSIS.
Clinical Obstetrics and Gynecology, 13: 178-201, 1970.
E - gen. pap. - gen. disc. - humans - chromosome damage - teratogenicity - intent. use - female consumpt. - male consumpt. -

chrom. aberr. - congenit. defects - fetal maldevel. - no effect B-2723.

The author presents a review of the literature concerning the diagnosis of genetic disorders by examining a sample of the amniotic fluid. Case reports are mentioned on the teratogenic and the chromosome damaging effects of LSD. One child born to LSD using parents suffered from the unilateral fibular aplastic syndrome. Chromatid breaks were later found in both parents and the child. Another child of parents who had taken LSD was found to have a 45, XX, G cell. The similarity of the chromosome breaks caused by LSD and large doses of radiation is noted. The suggestion is made that the examination of cells from the amniotic fluid might diagnose genetic disorders caused by LSD and help in proving if there is, indeed, a correlation between LSD and other drugs taken early in pregnancy and fetal malformations.

80. Gant, D. W., and Dyer, D. C.
D-LYSERGIC ACID DIETHYLAMIDE (LSD-25): A CONSTRICTOR OF HUMAN UMBILICAL VEIN.
Life Sciences, 10(4): 235-240, 1971.
E - res. pap. - in vitro - humans - teratogenicity - exper. admin. - single dose - placent. funct. - drug action - hypothesis B-2724.

An experiment was undertaken with eight helical strips of umbilical vein obtained within 40 minutes after normal deliveries. The tissues were equilibrated under tension for 1.5 to 2 hours in Krebs solution at 37°C. and constantly aerated with 5 percent CO_2 and 95 percent O_2. Serotonin and LSD were added to four strips each. At the lower concentrations of LSD, prolonged lag before initiation of contraction and irregularity of the contractile response were observed. Higher concentrations produced more rapid contraction that held relatively constant with time. The maximum contractile effect of LSD reached approximately 90 percent of the serotonin response. However, the evidence from the lower concentration responses indicates that the human umbilical vein is more sensitive to LSD. Graphs are presented. LSD is a potent vasoconstrictor which is more persistent than serotonin. Possibly, this constricting action could cause a decreased fetal blood flow through the placenta causing fetal hypoxia and its consequences.

81. Garson, O. M., and Robson, M. K.
STUDIES IN A PATIENT WITH ACUTE LEUKAEMIA AFTER LYSERGIDE TREATMENT.
British Medical Journal, 2(5660): 800-802, 1969.

E - gen. pap. - case rep. - humans - chromosome damage - therapeut. use - injection - extended use - male consumpt. - chrom. aberr. - carcinogen. effect - chrom. analysis, peripheral - chrom. analysis, bone mar. - lab. test B-2725.

A 23 year old man developed lymphoblastic leukemia eight months after the last of six doses of LSD injected intramuscularly to treat an obsessive compulsive neurosis. He may have had a predilection to malignancy (two sisters died of malignancies before the age of 3), but there were no chromosome abnormalities in the parents. Bone marrow chromosomes showed an unusual pattern and morphology with the chromosomes being contracted and the chromatids widely separated. There was no Ph^1-like chromosome as in the only other reported case of myeloblastic leukemia following LSD intake. Large cells with multiple micronucleoli were similar to those reported in other LSD users. The possibility that chromosome abnormalities may imply a leukemogenic effect, as in Bloom's syndrome and Fanconi's anemia, is discussed in the light of other evidence. Reports are cited concerning the effects of LSD on chromosomes in vitro and in vivo, and of congenital defects in children of users. The reporting of all cases of leukemia or congenital defects following LSD intake is urged, to establish whether the effects are causal.

82. Gayer, J., Srb, V., and Příbyš, R.
ÚČINKY LSD NA BUNĚČNÉ ÚROVNI A JEJICH MOŽNÝ VÝZNAM V LÉKAŘSTVÍ. [Effects of LSD at the cellular level and its possible significance in medicine.]
Časopis Lékařu Českých, 110: 176-179, 1971.
C - gen. pap. - gen. disc. - humans - chromosome damage - teratogenicity - chrom. aberr. - congenit. defects - no effect B-2726.

Whether LSD exerts damaging effects on the chromosomal apparatus of cells, both somatic and generative, cannot be said definitely. Likewise, it cannot be generally said that LSD has teratogenic, mutagenic, or cancerogenic effects although under certain experimental conditions these effects are quite apparent. There is enough evidence, however, to warrant the cautious use of this substance in medicine and psychiatry.

83. Geber, W. F.
CONGENITAL MALFORMATIONS INDUCED BY MESCALINE, LYSERGIC ACID DIETHYLAMIDE, AND BROMOLYSERGIC ACID IN THE HAMSTER.
Science, 158(3798): 265-267, 1967.
E - gen. pap. - in vivo - tables - hamsters - teratogenicity - exper. admin. - s. c. admin. - single dose - female consumpt. - congenit. defects - fetal maldevel. - litter - resorpt. rate - birth, pre term. B-2727.

Malformations of the brain, spinal cord, liver, and other viscera, along with body edema and localized hemorrhages, were found in fetal hamsters of females injected subcutaneously with a dose of either mescaline, LSD, or 2-bromolysergic acid diethylamide on the 12th day. About ten percent of the abnormal fetuses had more than one defect - several had four to five. All drugs produced an increase in the percentage of small fetuses, the number of resorptions, and fetal mortality. No major congenital abnormalities were found in the 300 offspring of the saline injected controls. Mescaline was a less potent teratogen than LSD and its 2-brom derivative as judged by the dose required to produce anomalies, but was equipotent in the type and number of abnormalities produced. This corresponds, qualitatively, to their relative psychotomimetic potencies. References to studies on the effects of LSD on pregnant rats and on chromosomes in human users are cited.

84. Geber, W. F., and Schramm, L. C.
EFFECT OF MARIHUANA EXTRACT ON FETAL HAMSTERS AND RABBITS.
Toxicology and Applied Pharmacology, 14: 276-282, 1969.
E - res. pap. - in vivo - tables - hamsters - rabbits - teratogenicity - exper. admin. - s. c. admin. - extended use - female consumpt. - congenit. defects - embryocidal - birth, pre term. - hypothesis B-2728.

Malformations of the brain, spinal cord, foreleg, and liver, as well as edema of the head and spinal region were found in fetal hamsters and rabbits from females subcutaneously injected with two variations of marijuana resin. One extract induced sedation in the females at about four hours after injection and the other induced spontaneous chatter in some. Reduction in locomotor activity of rabbits was noted for up to the first 24 hours. Pregnant hamsters received a total of 25 to 300 mg./kg. of extract during days 6 through 8 of gestation. Pregnant rabbits received a total of 130 to 550 mg./kg. during days 7 through 10 of gestation. There was a marked species specificity with respect to fetal resorption. The

extracts were embryocidal and increased the number of runts in fetal rabbits but were not embryocidal toward the fetal hamsters. On a weight basis, the teratogenicity of marijuana, when compared with that reported for other psychotomimetic agents, is low, but the types of congenital malformations are similar. The mechanism of production of embryopathies is unknown. It is postulated that the resin may activate the sympathetic nervous system so that released catecholamines may pass across the placenta and act directly or indirectly on the fetal tissues.

85. Geber, W. F., and Schramm, L. C.
HEROIN TERATOGENIC AND BEHAVIORAL ACTIVITY IN HAMSTERS.
Federation Proceedings; Federation of American Societies for Experimental Biology, 28(2): 262, 1969.
E - abst. - in vivo - hamsters - teratogenicity - exper. admin. s. c. admin. - single dose - female consumpt. - congenit. defects - litter - birth, pre term. B-2729.

Pregnant hamsters were injected subcutaneously with either 10, 40, or 100 mg./100 gms. body weight of heroin on the 8th day of gestation. Maternal behavior consisted of extreme slowing, and sometimes exaggeration, of all bodily movements. This lasted up to 30 hours after administration. The females were sacrificed on the 12th day of gestation. Litter size decreased as the dose of heroin increased. Exencephaly, cranioschisis, and spinal edema were the most common deformities found in the offspring. The number and type of anomalies did not correspond to dose level.

86. Geber, W. F., and Schramm, L. C.
TERATOGENICITY OF MARIHUANA EXTRACT AS INFLUENCED BY PLANT ORIGIN AND SEASONAL VARIATION.
Archives Internationales de Pharmacodynamie et de Thérapie, 177(1): 224-230, 1969.
E - res. pap. - in vivo - tables - hamsters - teratogenicity - s. c. admin. - extended use - female consumpt. - congenit. defects - fetal maldevel. - birth, pre term. B-1329.

Extracts of New Jersey (A) and Mexican (B) grown marijuana are evaluated for their CNS and teratogenic activity. Hamsters were subcutaneously injected on days 6, 7, and 8 of gestation. Neither extract affected the number of fetuses per litter, but edema of the head, upper spinal areas, and total body was common. Malformations of brain, spinal cord, foreleg, and liver also occurred. There was a difference in type of defects induced by extracts A and

B and more defects occurred in experiments undertaken from November to January than from May to September. Seasonal variations in congenital defects occur in humans. The relationship of active agents in smoke, compared to various extracts, is discussed. References to reports on the effects of marijuana on fertility, on congenital defects in rats, on runting in mice, and factors relating to the possible mechanism of action are cited. High concentrations of extract A had a calming effect on the females four hours after injection and lasted for about four hours. Extract B induced protesting chatter within 30 minutes of injection which lasted for several hours.

87. Geber, W. F.
BLOCKADE OF TERATOGENIC EFFECT OF MORPHINE AND DIHYDROMORPHINONE BY NALORPHINE AND CYCLAZOCINE.
Pharmacologist, 12(2): 296, 1970.
E - abst. - in vivo - hamsters - teratogenicity - exper. admin. - s. c. admin. - single dose - female consumpt. - congenit. defects - birth, pre term. B-2730.

Nine groups of pregnant hamsters were given subcutaneous injections as follows: 1) morphine alone, 300 mg./kg., 2) dihydromorphinone alone, 150 mg./kg., 3) nalorphine alone, 100 to 300 mg./kg., 4) cyclazocine alone, 50 to 100 mg./kg., 5) morphine preceded by nalorphine, 6) morphine preceded by cyclazocine, 7) dihydromorphinone preceded by nalorphine, 8) dihydromorphinone preceded by cyclazocine, and 9) a saline injected control. All injections of the narcotic antagonists preceded the narcotic agent by 20 minutes. Injections were made on the 8th day of pregnancy and the females were sacrificed and the fetuses examined on the 12th day. Morphine and dihydromorphinone produced an average of 33 percent and 45 percent of abnormal fetuses per litter. Exencephaly and cranioschisis were the most dominant anomalies. Nalorphine and cyclazocine produced a dose dependent blockade of the teratogenic action of both narcotic agents.

88. Geber, W. F., and Schramm, L. C.
TERATOGENIC POTENTIAL OF VARIOUS NARCOTIC AND NON-NARCOTIC ANALGESIC AGENTS.
In: Committee on Problems of Drug Dependence. Report of the Thirty-second Meeting, 16-18 Feb., 1970, Washington, D. C., pp. 6571-6577, 1970.
E - res. pap. - in vivo - tables - hamsters - teratogenicity - exper. admin. - s. c. admin. - single dose - female consumpt. - congenit. defects - fetocidal - birth, pre term. - hypothesis

B-1328.

The teratogenic potential of analgesic compounds was assessed after subcutaneous injection in hamsters on the 8th day of gestation and sacrificed on the 12th day. Tables detail the concentrations, litter size, number of resorptions, and the percentage of malformations for: saline injected controls, morphine, heroin, codeine, methadone, dilaudid, meperidine, propoxyphene, pentazocine, and cocaine injected animals. Exencephaly and cranioschisis were the predominant anomalies induced. Others, including multiple malformations, are listed. Each drug produced some abnormalities. Cocaine elicited the fewest while methadone and dilaudid were potent teratogenic agents. Mechanisms, applicable to any teratogen, might involve decrease in uteroplacental blood flow, fetal hypoxemia, activation of maternal nervous systems to release neurohormones, or adrenal catecholamines and corticosteroids which may interfere with RNA and DNA synthesis.

89. Gelehrter, T. D.
LYSERGIC ACID DIETHYLAMIDE (LSD) AND EXSTROPHY OF THE BLADDER.
Journal of Pediatrics, 77(6): 1065-1066, 1970.
E - gen. pap. - case rep. - humans - male - teratogenicity - intent. use - oral admin. - extended use - female consumpt. - male consumpt. - congenit. defects - birth, full term B-2731.

A case report is presented of an infant, the son of parents who had ingested LSD and other drugs at the time of conception, with the rare congenital defect of exstrophy of the bladder. The pregnancy and birth were normal and the child weighed five pounds, seven ounces at birth. He also had epispadias, widely separated pubic rami, and bilateral inguinal hernias. The mother had allegedly taken LSD 12 to 15 times prior to the first 2 1/2 months of pregnancy. The father had taken the drug on two occasions about three months before his son's conception. Reference is given to three reported cases of three different and individually rare congenital limb malformations in children born to mothers who ingested LSD during the first trimester of pregnancy.

90. Genest, P.
ÉTUDE CYTOGÉNÉTIQUE DES HALLUCINOGÈNES. ESSAI PRÉLIMINAIRE DE LA LYSERGAMIDE (LSD-25) SUR LA CULTURE DES LEUCOCYTES HUMAINS. [Cytogenetic study of the hallucinogens. Preliminary tests with lysergamide (LSD-25) on the culture of human leucocytes.]
Laval Médical, 40: 56-58, 1969.
F - res. pap. - in vitro - humans - chromosome damage - exper. admin. - single dose - chrom. aberr. - no effect B-2732.

Due to the controversy over the effects of LSD on chromosomes, the author reports the findings of his work on the effects of the drug on human leucocytes cultivated in vitro. Studies were done on the mitosis index and possible chromosome anomalies (both quantitatively and structurally). When the cells were placed in cultures with varying concentrations of LSD and its monobromal derivative, BOL, no significant chromosome breaks were noted with either of the drugs. It was noted, however, that the mitosis index increased in inverse proportion to the amount of LSD in the culture. The author discusses the possible reasons for the different results and feels that no precise conclusions can be drawn from a study of such limited size and duration.

91. Gilmour, D. G., Bloom, A. D., Lele, K. P., Robbins, E. S., and Maximilian, C.
CHROMOSOMAL ABERRATIONS IN USERS OF PSYCHOACTIVE DRUGS.
Archives of General Psychiatry, 24(3): 268-272, 1971.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - female consumpt. - male consumpt. - chrom. aberr. - chrom. analysis, peripheral - confound. agent. B-0834.

Chromosomes from peripheral blood leukocytes of 56 users (29 remale, 27 male) of psychoactive drugs were compared with those of 16 non drug users (9 female, 7 male). None admitted exposure to recent X-rays, other irradiation, or viral infection. Drug users were divided into five groups according to the types of drugs they primarily used as well as the types of drugs they secondarily used. There was no difference between the controls and the group one marijuana users. Groups two to five showed elevated incidences of chromosomal aberrations over that of the controls but no dicentric or chromatid exchange abnormalities were found. All other categories of aberrations showed increased incidences. These increases were not particular to any one group but were largely accounted for by a few individuals within each group with more than one aberration each. Although any or all of

these drugs could possibly damage chromosomes, as shown, it seems more likely that some other factor or factors common to drug users might be responsible.

92. Grace, D., Carlson, E. A., and Goodman, P.
DROSOPHILA MELANOGASTER TREATED WITH LSD: ABSENCE OF MUTATION AND CHROMOSOME BREAKAGE.
Science, 161(3842): 694-696, 1968.
E - gen. pap. - in vivo - tables - fruit flies - chromosome damage - exper. admin. - injection - single dose - male consumpt. - chrom. aberr. - spermatogen. effect - no effect B-2733.

Tests were designed to assay the sensitivity of the male Drosophila to LSD for all stages of the meiotic cycle. In none of the stages was LSD associated with chromosome breaks or mutation. This is in contrast to in vitro and some in vivo studies with humans. Details of three assay techniques for mutations and a table of the results are given. The translocation test for breakage was negative for all 4,205 progeny tested. LSD may be enzymatically degraded in Drosophila and not in mammals, or reports on humans in which there was no consistent relation of LSD concentration to breakage frequency may be in error. A variety of mutagens tested in the Drosophila have shown a dose-response relationship. A three step procedure for definitive analysis of genetic effects of chemicals is outlined.

93. Greenblatt, D. J., and Shader, R. I.
ADVERSE EFFECTS OF LSD: A CURRENT PERSPECTIVE.
Connecticut Medicine, 34(12): 895-902, 1970.
E - gen. pap. - review - fruit flies - humans - mice - mammals - rabbits - rats - chromosome damage - chrom. aberr. - congenit. defects - carcinogen. effect - no effect B-2734.

The author presents a review of the literature concerning the chromosome damaging effects and the teratogenicity of LSD under the headings: Cytogenetic Effects, Drosophila, Meiotic Chromosomes in Mice, Pregnancy in Animals, Human Leukocytes in Vitro, In Vitro Studies - Retrospective, In Vivo Studies - Prospective, Human Pregnancy, and Leukemia. Due to the flaws in the design of many of the studies, due to the contradictory results which have been obtained, and due to the fact that the results in most of these areas of investigation have little value in determining the possible teratogenic or mutagenic effect of LSD in humans, it cannot be confirmed or denied that LSD has an adverse cytogenetic effect.

94. Grossbard, L., Rosen, D., McGilvray, E., de Capoa, A., Miller, O., and Bank, A.
ACUTE LEUKEMIA WITH Ph^1-LIKE CHROMOSOME IN AN LSD USER.
Journal of the American Medical Association, 205(11): 791-793, 1968.
E - gen. pap. - case rep. - humans - chromosome damage - intent. use - extended use - male consumpt. - carcinogen. effect - chrom. analysis, peripheral - chrom. analysis, bone mar. - lab. test B-2735.

A case report is provided on a 19 year old freshman who was found to have acute leukemia and who had taken 15 doses of LSD ranging from 100 to 250 μg. along with other drugs. Some of his family members were known to have suffered from hereditary spherocytosis. A commentary is given of the symptoms which were present and of his responses to treatment along with the results of the many laboratory tests taken. No chromosome aberration, except for a Ph^1-like chromosome, was found in the patient's peripheral blood cells. The author states his reasons for diagnosing the illness as acute myelocytic leukemia. Only additional reports on the development of a Ph^1-like chromosome or leukemia in LSD users can establish a relationship between these entities and the use of LSD.

95. Hanaway, J. K.
EFFECT OF LSD ON THE DEVELOPING MAMMALIAN EMBRYO.
Psychopharmacological Bulletin, 5: 27, 1969.
E - abst. - in vivo - mice - rats - chromosome damage - teratogenicity - exper. admin. - single dose - female consumpt. - chrom. aberr. - congenit. defects - no effect - chrom. analysis, bone mar. B-2736.

Five μg./kg. of LSD was given to groups of pregnant rats and mice early or late in pregnancy. The females and the newborns were sacrificed at various time intervals to determine the teratogenic effect of LSD. Chromosomes of cells of embryos, fetuses, and adult animals were examined for aberrations. No congenital defects in the nervous system in mice or rats were found. A subcapsular cataract in mice injected before the 10th day of gestation was found. No chromosome anomalies were found in the bone marrow cells.

96. Hanaway, J. K.
LYSERGIC ACID DIETHYLAMIDE: EFFECTS ON THE DEVELOPING MOUSE LENS.
Science, 164: 574-575, 1969.
E - gen. pap. - in vivo - tables - mice - teratogenicity - exper. admin. - i. p. admin. - single dose - female consumpt. - congenit. defects - embryo. maldevel. - birth, pre term. B-2737.

Pregnant mice were intraperitoneally injected with 5 μg. of LSD on gestation days 6, 7, 8, or 9 and were sacrificed on day 18. The dose was 30 times that of the equivalent human hallucinogenic dose. The preparation of the embryos is described and a table of the results is given. Animals injected with LSD on the 6th day showed an 81 percent incidence of subcapsular lens abnormality compared to the controls; on the 7th day, 65 percent; on the 8th day, 55 percent; and on the 9th day, 79 percent. This subcapsular accumulation is different from a cataract in that it is not associated with changes in the lens fibers. It was the accumulation of a finely globular, eosinophilic substance outside the anterior lens epithelium, which remained normal, and under the capsule.

97. Hanifa Moursi, S. A., and Krause, D.
QUANTITATIVE STUDIES OF MORPHINE AND SOME OF ITS RELATED ALKALOIDS IN NEW-BORN MICE OF TOLERANT ANIMALS.
Journal de Pharmacologie, 3(4): 529, 1972.
E - abst. - in vivo - mice - teratogenicity - exper. admin. - extended use - female consumpt. - fetal maldevel. - birth, pre term. - birth, full term B-2738.

The effects of morphine and some of its related alkaloids on fetuses and new-born mice of females made tolerant to either morphine, levorphanol, dihydrocodeinone during pregnancy was studied. There was no difference in the number of litters or the body weight of the new-born mice except with the new-borns of morphine tolerant females which showed a decrease in body weight compared with the controls.

98. Harbison, R. D., and Mantilla-Plata, B.
PRENATAL TOXICITY, MATERNAL DISTRIBUTION AND PLACENTAL TRANSFER OF TETRAHYDROCANNABINOL.
Journal of Pharmacology and Experimental Therapeutics, 180(2): 446-453, 1972.
E - res. pap. - in vivo - mice - teratogenicity - exper. admin. - i. p. admin. - female consumpt. - stage of devel. - embryocidal -

fetal maldevel. - fetocidal - resorpt. rate - birth, pre term.
B-2739.

Pregnant mice were intraperitoneally injected with Δ^9-tetrahydrocannabinol in doses of 200 mg./kg. on days 8, 9, 10, 11, 12, or 13 of gestation and then sacrificed on day 19. Δ^9-THC-2,4-^{14}C was used to measure the maternal distribution, placental transfer, and excretion of Δ^9-THC. The resorption rate when the chemical was administered on days 8 and 9 was 68 percent and decreased to 27 percent when the chemical was administered on gestation days 12 and 13. A gestational period susceptibility was also present as THC significantly reduced the body weight of the surviving fetuses. The reduction was greater the later the treatment was given during gestation. The distribution and excretion of THC in the females is presented with charts and graphs. Only one-third of the small amount of Δ^9-THC found in the placenta tissue was measured in the fetal tissue. In addition, there were no significant differences in the amount of Δ^9-THC found in the fetus, amnionic fluid or complete conceptus. Possibly, the amnionic fluid may store Δ^9-THC and continuously expose the fetus to this compound.

99. Harpel, H. S., Jr., and Gautieri, R. F.
MORPHINE-INDUCED FETAL MALFORMATIONS. I. EXENCEPHALY AND AXIAL SKELETAL FUSIONS.
Journal of Pharmaceutical Sciences, 57(9): 1590-1597, 1968.
E - res. pap. - in vivo - tables - mice - teratogenicity - exper. admin. - s. c. admin. - single dose - female consumpt. - congenit. defects - fetal maldevel. - fetocidal - resorpt. rate - birth, pre term. B-2740.

Mice were subcutaneously given 100 mg./kg. of morphine sulfate on day 8 of gestation and there was no apparent effect on fetal development. Doses of 200 mg./kg. lowered the mean fetal weight, but no morphological abnormality was detected. With doses of 300 mg./kg., exencephaly was found in half of the litters. After doses of 400 and 500 mg./kg., exencephaly and axial skeletal fusions were found in a significant number of fetuses along with a decrease in the mean fetal weight and crown-rump length. All doses given on day 9 produced fusions in the axial skeleton and decrease in the mean fetal weight. The number of intrauterine deaths was increased significantly only in those females given 400 or 500 mg./kg. on day 9. In all morphine-treated groups, food consumption decreased significantly on the day of injection and, although fasting alone at this critical stage of pregnancy does affect embryonic development, it was evident that this was not primarily responsible for the teratogenic effects of morphine. Maternal effects included

stimulation followed by depression, and a hyperactive period of recovery up to 24 hours after the injection. At 400 or 500 mg./kg., some female deaths occurred. Based on the narrow range between the maternal LD_{50} and the teratogenic doses in this species, the teratogenic potential of morphine sulfate is low.

100. Hart, N. H., and Greene, M.
LSD: TERATOGENIC ACTION IN CHICK BLASTODERMS.
Proceedings of the Society for Experimental Biology and Medicine, 137(2): 371-373, 1971.
E - gen. pap. - in vitro - tables - mammals - teratogenicity - exper. admin. - single dose - congenit. defects - embryo. maldevel. B-2741.

LSD was administered in doses of 50 and 100 μg. to chick embryos cultured in vitro during stages 8 to 12 of gestation when fusion and regionalization of the neural tube, segmentation of the paraxial mesoderm, erythropoiesis, and fusion of the paired heart primordia occurred. Exposure did not increase mortality nor abnormally depress the growth of the chick embryos. There was a retardation in neural fold fusion, in some, while others showed a failure of the neural tube to fuse properly which was evident in both the brain and the spinal cord. There were also disturbances in the segmentation of the paraxial mesoderm and there was a significant reduction in the mean number of somites found per embryo. There was no interference with the regionalization of the brain or the primary optic vesicle formation. Nor was there a direct dose-response relationship found.

101. Hasleton, S.
MARIJUANA: A BRIEF REVIEW.
Australian and New Zealand Journal of Psychiatry, 6: 41-45, 1972.
E - gen. pap. - review - sec. disc. - humans - mammals - rabbits - rats - teratogenicity - exper. admin. - congenit. defects - no effect B-2742.

The author discusses the teratogenicity and the embryotoxicity of marijuana. Many of the problems in the research of this kind are the interspecies variability and the lack of specification of the extracts of the cannabis used. It has been found that anything above 25 mg./kg. of cannabis extract does have teratogenic effects on hamster fetuses. This dosage is comparable to a 140 pound girl taking 8 gm. of marijuana or smoking 8 'reefers'. The substance has been used for thousands of years. Human fetal susceptibility seems to be quite low and teratogenicity in humans is not clear. It

would seem, however, that smoking the drug during pregnancy is unwise.

102. Hecht, F., Beals, R. K., Lees, M. H., Jolly, H., and Roberts, P.
LYSERGIC-ACID-DIETHYLAMIDE AND CANNABIS AS POSSIBLE TERATOGENS IN MAN.
Lancet, 2(7577): 1087, 1968.
E - lett. ed. - case rep. - humans - teratogenicity - intent. use - extended use - female consumpt. - male consumpt. - congenit. defects - birth, full term - chrom. analysis, peripheral B-2743.

The case of a child born without a right hand is reported and the relevance to the mother taking LSD before pregnancy, and cannabis before and during pregnancy, is discussed. The father also used both drugs. The mother took three antinausea drugs as well. No chromosome breaks were seen in the mother's leukocytes six months after delivery and 14 months after her last intake of LSD. References are cited to reports on a baby of an LSD user born with fibular aplasia, and on experiments in the Drosophila, mice, and rats. Female rats were exposed to cannabis and 17 percent of their fetuses had phocomelia or amelia. Reporting of normal and malformed babies of LSD and cannabis users is urged since evidence of any relationship is scanty.

103. Hirschhorn, K., and Cohen, M. M.
NONPSYCHIC EFFECTS OF LYSERGIC ACID DIETHYLAMIDE.
Annals of Internal Medicine, 67(5): 1109-1111, 1967.
E - gen. pap. - gen. disc. - humans - rats - chromosome damage - exper. admin. - intent. use - oral admin. - chrom. aberr. - fetal maldevel. - fetocidal - carcinogen. effect - no effect - chrom. analysis B-2744.

The author found that 14 of 17 young adults who repeatedly ingested LSD had rates of chromosome breakage two to six times that of the controls. Dicentrics and exchange figures were observed in the users but were absent in the controls. Two children (one who was studied 2 1/2 years after birth) born to mothers who had taken 300 to 600 μg. of LSD showed three to five times as much chromosomal damage while two others, born to mothers who had taken 50 to 100 μg. doses, showed no significant increase. Animal studies have clearly shown the teratogenic potential of LSD. Based on comparisons with other syndromes and the effects of other drugs, it seems that a potential danger of LSD is the possible increase in the incidence of leukemia and other neoplasms in exposed persons. The greatest danger could lie, however, in the potential chromoso-

mal damage to the gametes, the consequences of which could not be determined for quite some time.

104. Hirschhorn, K., and Cohen, M. M.
DRUG-INDUCED CHROMOSOMAL ABERRATIONS.
Annals of the New York Academy of Sciences, 151: 977-987, 1968.
E - gen. pap. - in vitro - gen. disc. - tables - humans - chromosome damage - exper. admin. - intent. use - chrom. aberr. - chrom. analysis B-2745.

Irradiation, viruses, antimetabolites, and other chemicals induce chromosome damage, possibly by different mechanisms. A model for assay of potential teratogens is outlined to test their effects on mitosis; for scoring chromosome abnormalities, including chromatid breaks, dicentric and ring chromosomes, and translocation figures; and to note the incidence of polyploidy and/or endoreduplication. Figures and tables are presented. In vitro studies of the effects of LSD on chromosomes in leukocytes and in in vivo studies of 18 users showed a high percentage of breaks as did two children exposed in utero. Two other children of a mother who took only 50 to 100 μg. of LSD did not show a high incidence of chromosome breaks. Chlorpromazine had a transient effect while LSD had a longer lasting one. Potential dangers associated with chromosome anomalies include abortions, congenital defects, and neoplasms. References to other drugs and syndromes associated with chromosome anomalies and to animal experiments are cited.

105. Hoey, J.
LSD AND CHROMOSOME DAMAGE.
Journal of the American Medical Association, 212(10): 1707, 1970.
E - lett. ed. - gen. disc. - humans - teratogenicity - chrom. aberr. - congenit. defects - no effect B-2746.

The author feels that an interpretative note of caution should accompany articles dealing with such a volatile subject as LSD, particularly in regards to one case report published which was found to incorrectly imply that that case had proven that LSD deforms children of users. This misleading presentation could lead to an increase in the already broad credibility gap.

106. Hoffer, A.
EFFECT OF LSD ON CHROMOSOMES.
Canadian Medical Association Journal, 98: 466, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - intent.

use - chrom. aberr. - no effect B-2747.

The writer commends an editorial review of reports on LSD effects on chromosomes, on genetic damage, and on malformed fetuses. Mention of association of LSD with leukemia was justifiably omitted. He distinguishes between 'possibility' and 'probability' of LSD causing genetic harm (the latter being slight), and notes that one percent of all babies have some deformity. No malformed babies have been born to Saskatchewan women treated with LSD in concontrolled conditions. It has not been proven that LSD produces breaks in germinal tissue. Tranquillizers, viral infections, and radiation may produce chromosomal breaks in leukocytes, yet there is no association between tranquillizer medication and fetal abnormalities. Danger of psychosis alone, is sufficient to warrant publicity to deter illicit users. Other warnings of toxicity are premature and will destroy confidence in the authorities if proven false.

107. Houston, B. K.
REVIEW OF THE EVIDENCE AND QUALIFICATIONS REGARDING THE EFFECTS OF HALLUCINOGENIC DRUGS ON CHROMOSOMES AND EMBRYOS.
American Journal of Psychiatry, 126(2): 251-254, 1969.
E - gen. pap. - review - fruit flies - hamsters - humans - mice - rats - chromosome damage - teratogenicity - exper. admin. - intent. use - single dose - chrom. aberr. - congenit. defects - no effect - chrom. analysis B-1330.

Chromosomes in leukocytes have been examined after administration of LSD in vitro, in illicit users, and in those treated with pure LSD. Results are contradictory. A study of the effects on chromosomes in germ cells of mice was inconclusive. One experiment proved the mutagenic potential of LSD in Drosophila to be negative. Hallucinogenic drugs, on the basis of the evidence to date, do not cause chromosomal damager nor adversely affect the offspring as a result of chromosomal changes. However, embryos of mice, rats, and hamsters have been damaged by injections early in pregnancy. Mescaline also produced defects in hamster embryos. The crucial period (if extrapolation to humans is warranted) is between days 16 to 22 of pregnancy. Concern should be focused on effects in utero, not on mutant chromosomes in parents.

108. Hsu, L. Y., Strauss, L., and Hirschhorn, K.
CHROMOSOME ABNORMALITY IN OFFSPRING OF LSD USER. D TRISOMY WITH D/D TRANSLOCATION.
Journal of the American Medical Association, 211(6): 987-990, 1970.

E - gen. pap. - case rep. - humans - female - chromosome damage - teratogenicity - intent. use - female consumpt. - chrom. aberr. - congenit. defects - death - birth, full term - chrom. analysis, peripheral B-0727.

Multiple defects, including facial and skeletal anomalies compatible with the trisomy syndrome, were observed at birth and during autopsy of a girl who died nine hours after birth. A detailed cytogenic report noted a D/D translocation. In the mother's lymphocytes only one break was seen but two cells had an abnormally short C group chromosome. The father had one chromatid break and two cells with strikingly unpaired chromosomes in the C group. The D/D translocation was not seen in either parent. LSD may have damaged the germ cells prior to fertilization. The mother had taken LSD three times nine months prior to conception and once three years earlier. She took barbiturates, marihuana, and methedrine during pregnancy. The father had taken LSD four years prior to the birth and used marihuana and dexedrine. Reports of in vitro and in vivo studies on teratogenic effects of LSD are discussed. D/D translocation is rare unless one parent is a carrier. Its association with trisomy in this case could be coincidental; the other drugs used may have been involved, but LSD seems the most likely cause.

109. Hultén, M., Lindsten, J., Lidberg, L., and Ekelund, H.
STUDIES ON MITOTIC AND MEIOTIC CHROMOSOMES IN SUBJECTS EXPOSED TO LSD.
Annales de Génétique, 11(4): 201-210, 1968.

E - res. pap. - case rep. - in vivo - tables - humans - female - chromosome damage - intent. use - oral admin. - extended use - female consumpt. - male consumpt. - chrom. aberr. - no effect - birth, full term - chrom. analysis, peripheral B-2748.

An experiment was undertaken in which chromosome analyses were performed on a newborn girl exposed in utero to LSD and her parents who both used LSD. In addition, chromosome analyses were done on the germ line cells in two men, one of whom had been heavily exposed to the drug. Blood cultures from the parents and the child were harvested after 72 hours and testicular biopsies were performed on the two men. Short case reports and karyotype photographs are provided for the five subjects. The child was the

only one who had mitotic chromosome abnormalities but these appeared at five weeks of age and not again at eight months. The researchers found that few spermatogonial metaphases could be counted with accuracy. The one man who had consumed about 30,000 μg. of LSD over six months showed a significant increase in polyploid cells, but only on one of two occasions. There was no increased frequency of chromosome breakage but a few chromosome interchanges were found. These interchanges are usually quite rare. On the basis of these five persons, there seems to be little support that LSD causes chromosome damage.

110. Hungerford, D. A., Taylor, K. M., Shagass, C., LaBadie, G. U., Balaban, G. B., and Paton, G. R.
CYTOGENETIC EFFECTS OF LSD 25 THERAPY IN MAN.
Journal of the American Medical Association, 206(10): 2287-2291, 1968.
E - res. pap. - in vivo - tables - humans - chromosome damage - therapeut. use - injection - extended use - chrom. aberr. - chrom. analysis, peripheral B-2749.

Chromosomes from leukocytes of four patients receiving three doses each, one to three weeks apart, of usually 200 μg. of LSD intravenously showed some increase in the aberration frequency immediately after the second and third doses. Dicentrics and multiradial aberrations were present only after therapy. However, in three patients there was a return to control levels between one and six months after the final dose. In the fourth, a control sample had not been taken. The frequency of aberrations was high for that patient but probably due to his occupational exposure to radiation. Explanations for conflicting results of others in vitro and in vivo include different laboratory techniques, unreliable estimates of dose taken by illicit users, possible effects of poor nutrition and infection, and possible synergistic effects in multiple drug users. Criticism of various studies on effects of LSD therapy is noted. Carcinogenesis and teratogenesis have been linked to LSD, but are unproven in humans. Although LSD in therapy is considered safe, cytogenic hazards from drug abuse are not discounted.

111. Idänpään-Heikkilä, J. E., and Schoolar, J. C.
^{14}C-LYSERGIDE IN EARLY PREGNANCY.
Lancet, 2(7613): 221, 1969.
E - lett. ed. - in vivo - hamsters - chromosome damage - teratogenicity - exper. admin. - i. p. admin. - s. c. admin. - single dose - female consumpt. - stage of devel. - birth, pre term. - lab. test B-2750.

Groups of pregnant hamsters were intraperitoneally injected with either 5 or 500 μg./kg. of radioactive LSD on the 5th and 6th or the 15th and 16th day of pregnancy. The animals were killed by bleeding at different times up to 24 hours after injection and both the total radioactivity and the unchanged C-LSD were measured in the fetuses, placentas, and maternal blood and brain. It was evident that LSD easily crossed the placenta in the young hamster fetuses and much more slowly during the last week of gestation. It would seem that the effect of LSD on chromosomes of the fetuses exposed in utero could be due to the direct action of LSD.

112. Idänpään-Heikkilä, J. E., and Schoolar, J. C.
LSD: AUTORADIOGRAPHIC STUDY ON THE PLACENTAL TRANSFER AND TISSUE DISTRIBUTION IN MICE.
Science, 164: 1295-1297, 1969.
E - res. pap. - in vivo - mice - teratogenicity - exper. admin. - injection - female consumpt. - male consumpt. - stage of devel. - birth, pre term. B-2751.

Radioactive LSD was intravenously injected into four males and six pregnant mice. The females were killed at different times up to 120 minutes after injection by freezing. The autoradiographic study methods are described. It was found that LSD easily diffuses and penetrates the cell membranes. The amount of radioactivity was higher in the brain and myocardium, and much higher in the adrenals, hypophysis, kidneys, liver, lungs, bone marrow, and lymphatic tissue compared to the blood. These findings were made five minutes after injection. Late in pregnancy, 0.5 percent (70 percent of this being unchanged ^{14}C-LSD) of the administered radioactivity traversed the placenta. The penetration rate of LSD through the placental barrier seemed to be greater during the first trimester of pregnancy reaching 2.3 percent that in the mother. The greatest radioactivity concentration in the fetal organs was found at 30 minutes after injection with a significant amount remaining for at least two hours.

113. Idänpään-Heikkilä, J. E.
LSD: N VAIKUTUS KROMOSOMEIHIN JA SIKIÖÖN. [LSD: Effect on chromosomes and fetus.]
Duodecim, 85: 274-282, 1969.
Fi - gen. pap. - gen. disc. - fruit flies - humans - mice - hamsters - rats - chromosome damage - teratogenicity - chrom. aberr. - congenit. defects - carcinogen. effect - placent. funct. - no effect B-2752.

The effects of LSD on chromosomes and on fetuses are still in doubt. It has been shown that pure LSD can produce chromosomal aberrations in vitro and possibly in vivo. Illicit LSD seems to have even more potential for causing damage. Cytogenetic damage has been found in cultured human leucocytes, in Drosophila, and in the meiotic cells of mice. There has not been found any dose-response relationship in regards to the LSD use and chromosome damage in man. The varied doses, the impurity of illegal LSD, and the use of other drugs may be the reasons for this discrepancy. Most laboratory animals have shown an increase in congenitally malformed fetuses when treated early in pregnancy. The carcinogenic effect of LSD is highly questionable. In general, there does appear to be some cytogenetic risk involved in the use of LSD.

114. Idänpään-Heikkilä, J., Fritchie, G. E., Englert, L. F., Ho, B. T., and McIsaac, W. M.
PLACENTAL TRANSFER OF TRITIATED-1-Δ^9-TETRAHYDRO-CANNABINOL.
New England Journal of Medicine, 281: 330, 1969.
E - lett. ed. - in vivo - hamsters - teratogenicity - exper. admin. - i. p. admin. - s. c. admin. - single dose - female consumpt. - stage of devel. - placent. funct. - birth, pre term. B-2753.

In this correspondence, the author reports an experiment undertaken with groups of pregnant hamsters and cannabis extract. Two mg./kg. was intraperitoneally or subcutaneously administered on the 6th day or the 15th day of gestation. The females were then killed at different times up to 24 hours after injection. The fetuses, placentas, maternal blood, and brain were homogenized in water, and their radioactivity was assayed. Radioactivity crossed the placenta within 15 minutes reaching a peak in the fetus at 30 minutes. Fetuses from females injected early in pregnancy contained about three times more radioactivity than fetuses exposed late in pregnancy. THC crosses the placenta and this may exert a direct action on the developing fetus.

115. Idänpään-Heikkilä, J. E., J. E., Schoolar, J. C., and Allen, A.
TOTAL BODY KINETICS AND PLACENTAL TRANSFER OF LABELED LSD IN MICE.
In: Harris, Robert T., et al. (Eds.). Drug Dependence. The University of Texas Press, Austin, pp. 55-66, 1970.
E - book - in vivo - mice - teratogenicity - exper. admin. - injection - single dose - female consumpt. - stage of devel. - placent. funct. - birth, pre term. B-2754.

Total body autoradiographic method, liquid scintillation, and thin layer chromatography techniques were used to determine possible accumulation sites that might explain the pharmacological or cytotoxic effects of LSD. In addition, whether LSD or its metabolites penetrated the mouse placenta, the rate and amount of such transfer, and the difference in penetration between early and late stages of pregnancy were studied. Figures showing the distribution of radioactivity in the female mouse and the fetus are given. High concentrations of LSD were found in the female's brain, adrenal glands, thalamus, hippocampus, and the endocrinologically active tissue. The distribution pattern of C-LSD in the fetuses was similar to that in the mother. The blood had a low amount of radioactivity, indicating a rapid transport of LSD into the tissues, with the highest amounts being found in the lung, liver, intestine, brain, and myocardium, in that order. The uptake in the placenta was highest five minutes after injection and the greatest radioactive concentration in the fetal organs was found at 30 minutes. The accumulation of radioactivity in the young embryo is about four times higher than in the nearly completely developed fetus.

116. Irwin, S., and Egozcue, J.
CHROMOSOMAL ABNORMALITIES IN LEUKOCYTES FROM LSD-25 USERS.
Science, 157(3786): 313-314, 1967.
E - gen. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - chrom. aberr. - chrom. analysis, peripheral B-2755.

There was a significant increase in the number of cell abnormalities and chromosome breaks in leucocytes in only one of nine control subjects but in six of eight LSD users, none of whom had recent X-rays, but who had used cannabis (mescaline or peyote), psilocybin or dimethyltryptamine. The mean estimated single dose was 200 to 600 μg. at 4 to 200 doses per person giving a total of between 400 to 2800 μg. The percentage of abnormalities seemed unrelated to size or number of doses except that the two users with a normal number of breaks took about 200 μg. per dose while the others took 300 or more μg. Quadriradials and increased chromosomal breaks observed are also characteristic of Fanconi's anemia and Bloom's syndrome - both associated with neoplasia. The Ph_1 chromosome which is associated with leukemia was also seen. Chromosome abnormalities appear to be induced by as little as four doses of LSD at a minimum of 200 μg. per dose.

117. Irwin, S., and Egozcue, J.
CHROMOSOME DAMAGE NOT FOUND IN LEUKOCYTES OF CHILDREN TREATED WITH LSD-25.
Science, 159(3816): 749, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - chrom. aberr. - no effect B-2756.

The authors explain that their previous experiment was done to determine if the reported findings in vitro were relevant to the use of the drug in vivo. They acknowledge that no evidence has been presented showing chromosomal damage after pure LSD administration. However, from what has been found from in vitro studies and due to the lack of data, LSD cannot be ruled out as being dangerous either. In an experiment which gave conflicting results, low doses of LSD (100 to 150 μg.) were given and only ten metaphases per patient were studied. The life cycle of the circulating lymphocyte is believed to be two years so that drug effect studies must be undertaken in an interval not greater than this time since the last exposure to the drug.

118. Iuliucci, J. D., and Gautieri, R. F.
MORPHINE-INDUCED FETAL MALFORMATIONS II: INFLUENCE OF HISTAMINE AND DIPHENHYDRAMINE.
Journal of Pharmaceutical Sciences, 60(3): 420-425, 1971.
E - res. pap. - in vivo - tables - mice - teratogenicity - exper. admin. - s. c. admin. - female consumpt. - congenit. defects - fetal maldevel. - birth, pre term. B-2757.

Pregnant mice were put into one of the following seven treatment groups: saline control; morphine-treated group; antihistamine diphenhydramine HCl-treated group; histamine dihydrochloride-treated group; diphenhydramine HCl- followed by injection of morphine-treated group; histamine- followed by injection of morphine-treated group; and saline- followed by injection of morphine-treated group. All drugs were subcutaneously administered on either day 8 or day 9 of gestation and the females were sacrificed on day 18. All the results are presented in tables. The maternal effects of the drugs and the combinations of drugs are given. There were no significant differences among the resorption ratios in any of the test groups. The lowest dose of morphine caused a significant decrease in the mean fetal weight. In the groups treated with 300 mg./kg. of diphenhydramine and 200 mg./kg. of morphine, more exencephalic fetuses resulted than with morphine alone. With morphine, cryptorchid testes were found along with only a few other soft-tissue malformations. 300 and 400 mg./kg. of morphine produced a significant occurrence of rib and vertebral fusions.

When combinations of morphine and diphenhydramine were given, there was an enhancement in the ability of morphine to induce both exencephaly and axial skeletal fusions.

119. Jacobson, C. B., and Magyar, V. L.
GENETIC EVALUATION OF LSD.
Clinical Proceedings of Children's Hospital of the District of Columbia, 24: 153-161, 1968.
E - gen. pap. - gen. disc. - humans - chromosome damage - oral admin. - chrom. aberr. - embryocidal - carcinogen. effect - no effect B-2758.

The genetic effect of LSD should be well investigated because it has been found to be similar to other mutagenetic agents and is the only agent known to be indiscriminantly used by people at the reproductive age in life. The authors have found chromosomal damage in the cultures of over 50 LSD users. The importance of having a good mutagenetic test system for evaluating the effects of any mutagen is mentioned. The somatic effects of these agents, such as the ageing of cells and the increased incidence of malignancy in tissues with a short cellular life span, are discussed. Premature ageing of cells has been found with LSD. A carcinogenic effect with LSD has not been determined. However, the Philadelphia chromosome, which has been associated with leukemia, has been observed in many LSD patients. The gestational effect of any mutagen could result in an embryotoxic or a mutagenic consequence. This effect in connection with LSD has been found in two early human abortuses and has been confirmed by other studies. LSD appears to be teratogenic if taken in sufficient doses during the critical stages of pregnancy. LSD users have shown a low fertility and poor reproductive ability. In newborn children of parents who had taken LSD it seems that the chromosomal breakage found has little consequence and undergoes repair in a short period of time.

120. Jacobson, C. B., Stubbs, V., and Berlin, C. M.
THE PERINATAL ASSESSMENT OF A POSSIBLE MUTAGEN LSD-25.
Southern Medical Journal, 61(12): 1328, 1968.
E - abst. - in vivo - humans - chromosome damage - intent. use - chrom. aberr. - chrom. analysis, peripheral - lab. test B-2759.

The authors are undertaking a prospective study to determine the reproductive consequences of LSD use. Adults are accepted into the study when they have revealed a history of LSD use which has been supported by both leucocyte and fibroblast chromosomal culture

analyses. Aneuploidy and aberration rate must be found to be three times greater than the normal range. The study of these adults and their offspring are begun before birth, at delivery, and for many years after. The evaluation consists of fetal ECGs, chromosomal analysis, amniotic fluid analysis, and pediatric followup. Of the 15 mothers studied to date, 11 showed severe and 3 showed moderate chromosomal damage. Three newborns showed severe and 3 others showed moderate chromosomal damage. However, most of the children showed repair of the chromosomal damage in later examinations. There was not a significant increase in the number of congenital defects found in the young.

121. Jacobson, C. B., Arias-Bernal, L., Vosbeck, E., DelRiego, A., Ahearn, K., and Magyar, V.
CLINICAL AND REPRODUCTIVE DANGERS INHERENT IN THE USE OF HALLUCINOGENIC AGENTS.
In: Sunderman, F. W., and Sunderman, F. W., Jr., eds., Laboratory Diagnosis of Diseases Caused by Toxic Agents.
St. Louis: Warren H. Green, Inc., 220-230, 1970.
E - book - in vivo - tables - humans - chromosome damage - intent. use - female consumpt. - abort. rate - chrom. aberr. - chrom. analysis, peripheral - lab. test B-2760.

The utilization of the chromosom[illegible] for the standard of [illegible] assay, as well as the clinical significance of chromosomal aberrations, is discussed in connection with a retrospective study. The chromosomes of peripheral blood and skin cultures from 66 adults, 16 neonates, and 21 abortuses who had taken LSD or were exposed to it in utero were analysed. The clinical interpretations of the chromosomal markers such as dicentrics, rings, and quadriradial exchanges were found in the LSD users. Gradual repair was present in one subject until a second dose of LSD was taken. The relatively high mutagenic level seen in the skin and amnion tissue indicated an increased sensitivity and a longer repair period after the second experience. One abortus was found to have CNS and cardiac defects. Others showed a midline defect in the occipital region of the neuro-cranium. Other forms of neural tube closure defects seemed to resemble a form of exencephaly with failure in the roof of the diencephalon. It was noted that there was a retardation or a decreased growth rate found in the chromosome cultures.

122. Jacobson, C. B., and Berlin, C. M.
POSSIBLE REPRODUCTIVE DETRIMENT IN LSD USERS.
Journal of the American Medical Association, 222(11): 1367-1373, 1972.
E - gen. pap. - in vivo - tables - humans - female - male - chromosome damage - teratogenicity - intent. use - oral admin. - extended use - female consumpt. - male consumpt. - stage of devel. - abort. rate - congenit. defects - death - embryocidal - confound. agent B-2761.

A study was undertaken with 140 pregnant women and their consorts who had admittedly taken LSD before or after conception. This involved 148 pregnancies. Half of the adults were found to have taken between 2 and 20 doses of LSD. Many of these subjects also gave a history of the use of other illicit drugs. There were 53 therapeutic and 12 spontaneous abortions. Eighty-three pregnancies ended with live newborn infants, 75 of these normal, one born prematurely and died, and eight others who had major congenital anomalies. Case reports are provided for the 8 infants with congenital damage. Fourteen of the therapeutic abortuses were intact enough for analysis. Four of these embryos were defective with midline fusion defects being the most prominent. Of the seven spontaneous abortuses examined, four fetuses showed encephoceles and failure of skeletal development of the extremities. In the newborns, there was no evidence of cellular ageing. They showed normal growth and development up to the last examination at 2 years of age. The congenital anomalies found in the 8 newborns were described to be chiefly on the CNS. It was found that half of the newborns had abnormal chromosomes that repaired themselves by the age of 3 to 6 months. Eight of 12 women in the original group of women were unable to conceive for at least the past 18 months. The results suggest that LSD might be hazardous to human reproduction.

123. Jagiello, G., and Polani, P. E.
MOUSE GERM CELLS AND LSD-25.
Cytogenetics, 8: 136-147, 1969.
E - res. pap. - in vivo - in vitro - tables - mice - chromosome damage - exper. admin. - s. c. admin. - single dose - extended use - female consumpt. - male consumpt. - chrom. aberr. - spermatogen. effect - no effect - chrom. analysis B-2762.

Experiments were undertaken to assess the acute and chronic effects of LSD on germ cells of a non-inbred strain of mice. Four groups of 6 animals each were subcutaneously injected each day with .5, 1, 2.5, and 5 μg./kg. of freshly prepared LSD for 31 days.

Four of the 6 animals in each group were killed on days 32, 40, 47, and 54 and meiotic preparations were made. The serial sections of testes were studied. Bone-marrow of the two additional animals in each group was obtained on days 32 and 54 and was examined. In the acute experiments, six mice were given single subcutaneous doses of 1 g./gm. of LSD. The animals were killed for meiotic study 12 to 66 hours thereafter. In a third experiment, ova from adult dioestrous females were incubated in medium containing .01 to 75 μg./ml. of LSD for five hours in an in vitro study. Meiotic preparations from the females and spermatogonial and bone-marrow metaphases were studied for numerical and structural errors. The chronic experiments showed no effect attributable to length of exposure or dose when compared with the controls. Tables are provided. There were no signs of chromosomal rearrangements. In the bone-marrow studies, there were no breaks, gaps, or other structural changes. Karyotype figures are presented. The acute treatment of females with doses of .5 to 30 μg. per day had no effect on meiosis of ova obtained from superovulation. In addition, the meiotic figures from the 65 day old females given a single injection on day 21 of gestation were normal. Meiotic studies in males and females give comparable results. LSD does not appear to produce chromosome abnormalities in the germ cells of mice.

124. Jarvik, L. F., Kato, T., Saunders, B., and Moralishvili, E.
LSD AND HUMAN CHROMOSOMES.
Preprint. Paper presented at the sixth annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, 8pp., 1967.
E - gen. pap. - in vitro - tables - humans - chromosome damage - exper. admin. - single dose - chrom. aberr. - chrom. analysis, peripheral B-2763.

Reports of in vitro and in vivo studies on the effects of LSD on chromosomes are cited. Details of the results from previous experiments are given. New results are reported which agree, essentially, with the published data in that a breakage rate of 4.7 percent was observed in the controls while an average breakage rate of 10.0 percent was found when LSD was added in vitro to blood. Two cultures did not correspond to LSD and it is such individual differences that may account for the divergent results in in vivo studies. LSD, aspirin, and ergonovine maleate all produce breaks in excess of the controls but to a lesser extent than does streptonigrin. Caffeine reportedly affects chromosomes and is discussed along with chlorpromazine and other agents. Caution is urged in expecting in vitro results to correspond with in vivo results. The intact organism has evolved mechanisms for detoxica-

tion, X-rays, viruses, and various chemical mutagens which affect chromosomes. Perhaps any agent, given critical timing and dose, may be a teratogen.

125. Jarvik, L. F.
CONTRADICTIONS IN LSD RESEARCH.
Science, 162: 621, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - chrom. aberr. - no effect B-2764.

The writer points out the divergent points of view concerning the genetic hazards of LSD. While one study seems to imply that it has been scientifically proven that LSD causes chromosome damage in man, other researchers question the predicted consequences to LSD users and their offspring and have demonstrated that chromosomal damage can be caused by more commonly used agents. More evidence must be found before any conclusions can be given.

126. Jarvik, L. F., and Kato, T.
IS LYSERGIDE A TERATOGEN?
Lancet, 1(7536): 250, 1968.
E - lett. ed. - in vitro - chromosome damage - exper. admin. - single dose - chrom. aberr. - no effect - chrom. analysis B-2765.

The commonly used oxytocic ergometrine maleate (lysergic-acid hydroxyisopropylamide), ergonovine maleate, and aspirin induce as many chromosomal aberrations as does LSD when added to human leucocytes in vitro. Streptonigrin induces more, giving a breakage rate of 35 percent compared to 10.2 percent for LSD. These results warrant a reappraisal of potential hazards of compounds hitherto considered innocuous. They may account for some unexplained fetal wastage, neonatal morbidity and mortality, and adult neoplasia. There is evidence on a relation between chromosome breaking ability and neoplasia. However, leucocytes are expendable, and the intact human organism can eliminate damaged somatic cells or gametes. It may be rare for agents inducing chromosome abnormalities in vitro to be carcinogenic or teratogenic.

127. Jarvik, L. F., Kato, T., Saunders, B., and Moralishvili, E.
LSD AND HUMAN CHROMOSOMES.
In: Efron, D. H., Cole, J. O., Levine, J., and Wittenborn, J. R., eds., Psychopharmacology: A Review of Progress, 1957-1967.
U. S. Public Health Service Publication, No. 1836, 1247-1252, 1968.

E - gen. pap. - in vitro - tables - humans - chromosome damage - exper. admin. - single dose - chrom. aberr. - chrom. analysis, peripheral B-2766.

Reports of in vitro and in vivo studies on the effects of LSD on chromosomes are cited. Details of the results from previous experiments are given. New results are reported which agree, essentially, with the published data in that a breakage rate of 4. 7 percent was observed in the controls while an average breakage rate of 10. 0 percent was found when LSD was added in vitro to blood. Two cultures did not correspond to LSD and it is such individual differences that may account for the divergent results in in vivo studies. LSD, aspirin, and ergonovine maleate all produce breaks in excess of the controls but to a lesser extent than does streptonigrin. Caffeine reportedly affects chromosomes and is discussed along with chlorpromazine and other agents. Caution is urged in expecting in vitro results to correspond with in vivo results. The intact organism has evolved mechanisms for detoxication, X-rays, viruses, and various chemical mutagens which affect chromosomes. Perhaps any agent, given critical timing and dose, may be a teratogen.

128. Jarvik, L.
DISCUSSION OF "COMPARISON OF CHROMOSOMAL PATTERNS OBTAINED FROM GROUPS OF CONTINUED USERS, FORMER USERS, AND NON-USERS OF LSD-25."
American Journal of Psychiatry, 126(5): 633-635, 1969.
E - gen. pap. - in vitro - humans - chromosome damage - exper. admin. - chrom. aberr. - no effect - chrom. analysis B-2767.

The author states that numerous studies have failed to show an increase in chromosomal damage due to LSD. It was noted that three patients admitted with psychotic reactions following the use of LSD along with other drugs showed no increase in chromosomal breaks. The importance of previously reported in vitro changes attributable to LSD was greatly reduced by an experiment undertaken. LSD was compared with three other compounds: ergonovine maleate, aspirin, and streptonigrin. LSD, ergonovine maleate and aspirin all doubled the control rate of chromosomal damage. However, streptonigrin caused seven times as many breaks as were found in the control cultures. This study showed that commonly used substances cause as much, and even more, chromosomal damage than LSD. The contradictory results of several studies are discussed. The in vitro technique of research is very complex and the difficulties of its use are discussed. The many factors which influence chromosome breakage are discussed. Differences

in medium, strains, use of antibiotics, and methods of distilling water all influence the percentage of breaks found in the cultures. It is true that there exist large individual differences in susceptibility of people to the chromosomal breaking action of various agents. The ideal type of research technique would be similar to a double blind, longitudinal study in which the subjects serve as their own controls.

129. Jeanbart, P., and Bérard, M. J.
À PROPOS D'UN CAS PERSONNEL DE MALFORMATIONS CONGÉNITALES POSSIBLEMENT DUES AU LSD-25. REVUE DE LA LITTÉRATURE. [With reference to a personal case of congenital malformations possibly induced by LSD-25. Review of the literature.]
L'Union Médicale du Canada, 100(5): 919-929, 1971.
F - gen. pap. - case rep. - review - humans - chromosome damage - teratogenicity - intent. use - chrom. aberr. - congenit. defects - carcinogen. effect - chrom. analysis B-2768.

The author suggests points of consideration which could prove useful in dispelling some of the discrepancies which exist in the results of various studies on the teratogenic effect of LSD. He feels one should concentrate on the most convincing of the literature already presented in this field, and from this, furnish more arguments in the pursuit of this research. He cites the numerous chromosome studies which have been done. With regard to the teratogenic effects of LSD, the studies are less numerous, but still contradictory. The case history is presented of a child born with malformations of the hands and feet who was born to parents who had taken LSD during the pregnancy. Although he does not feel that LSD has the same teratogenic power as thalidomide, he stresses the possibility of a teratogenic effect.

130. Jeanbart, P., and Bérard, M. J.
MALFORMATIONS CONGÉNITALES QUI POURRAIENT ÊTRE ATTRIBUÉES AU LSD-25. REVUE DE LA LITTÉRATURE À PROPOS D'UN CAS PERSONNEL. [Possible congenital malformations induced by LSD-25. Review of the literature with reference to a personal case.]
Gynécologie et Obstétrique, 70: 215-230, 1971.
F - gen. pap. - case rep. - review - humans - chromosome damage - teratogenicity - intent. use - chrom. aberr. - congenit. defects - carcinogen. effect - chrom. analysis B-2769.

The author suggests points of consideration which could prove use-

ful in dispelling some of the discrepancies which exist in the results of various studies on the teratogenic effect of LSD. He feels one should concentrate on the most convincing of the literature already presented in this field, and from this, furnish more arguments in the pursuit of this research. He cites the numerous chromosome studies which have been done. With regard to the teratogenic effects of LSD, the studies are less numerous, but still contradictory. The case history is presented of a child born with malformations of the hands and feet who was born to parents who had taken LSD during the pregnancy. Although he does not feel that LSD has the same teratogenic power as thalidomide, he stresses the possibility of a teratogenic effect.

131. Jensen, B., and Bro-Rasmussen, F.
LSD'S VIRKNING PÅ MUSEFOSTRE. [Effect of LSD on embryo mice.]
Ugeskrift For Laeger, 133(6): 237-239, 1971.
S - res. pap. - in vivo - tables - mice - teratogenicity - exper. admin. - injection - female consumpt. - stage of devel. - congenit. defects - resorpt. rate - birth, pre term. B-2770.

The teratogenic effect of various substances, including LSD, was investigated. Pregnant mice received injections of LSD at various times during gestation. There was a 14 percent resorption rate. Of the 784 embryos removed from the 68 female controls, 15 percent were found to be deformed. The incidence of deformity was greatest following injection near the middle of pregnancy. Also, when the injection was given at this time, there was a moderate increase in the incidence of resorption.

132. Jóhannesson, T., and Becker, B. A.
THE EFFECTS OF MATERNALLY-ADMINISTERED MORPHINE ON RAT FOETAL DEVELOPMENT AND RESULTANT TOLERANCE TO THE ANALGESIC EFFECT OF MORPHINE.
Acta Pharmacologica et Toxicologica, 31: 305-313, 1972.
E - res. pap. - in vivo - tables - rats - teratogenicity - exper. admin. - s. c. admin. - extended use - female - consumpt. - no effect - birth, pre term. - birth, full term B-2771.

Groups of female rats were subcutaneously injected with 20 ml./kg. of morphine sulfate on days 2 to 5, 7 to 9, or 11 to 13 of gestation and sacrificed. The fetuses were removed and examined with the results being presented in table form. Ten percent of the females died following the injection of morphine. There was no significant difference in the number of implants per litter from that of the

controls or in body weights and measurements of the fetuses. Some females were allowed to deliver their young for the analgesic part of the experiment. It was found that daily doses of morphine given late in pregnancy leads to tolerance of the analgesic action of morphine in both the females and the offspring. However, this tolerance was much more pronounced in the maternal rats.

133. Judd, L. L., Brandkamp, W. W., and McGlothlin, W. H.
COMPARISON OF THE CHROMOSOMAL PATTERNS OBTAINED FROM GROUPS OF CONTINUED USERS, FORMER USERS, AND NONUSERS OF LSD-25.
American Journal of Psychiatry, 126(5): 626-635, 1969.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - oral admin. - extended use - female consumpt. - male consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2772.

An experiment was undertaken with heavy users of LSD, users of LSD who had ceased using it, and control group of non-users. The purpose of the experiment was to determine if the chromosomal changes attributable to LSD ingestion were of a permanent nature or whether they disappeared after the cessation of drug use. Chromosomal analysis was performed on white blood cells of all the subjects. For the continuing users, it was a medium of one month prior to the drawing of the blood samples since they had last used LSD while the medium for the discontinued users was 24 months. Observations were made of well spread metaphasic cells, 35 of which were randomly selected from each subject. Chromosome analysis of the cells from all three groups revealed no observable variation from the normal male and female patterns. The continued users had a mean breakage frequency of 0. 32 percent of 315 cells scored. The discontinued group had a mean breakage frequency of 1. 8 percent of 280 cells analysed while the controls had a mean breakage frequency of . 72 percent of 280 cells scored. The experiment did not demonstrate an increase in chromosomal damage in subjects who were heavy users of LSD.

134. Kalia, C. S., Singh, M. P., Jain, H. K., and Katiyar, R. K.
LSD INDUCED GENETIC DAMAGE IN BARLEY.
Chromosoma, 32(2): 142-151, 1970.
E - res. pap. - in vivo - tables - plants - chromosome damage - exper. admin. - extended use - chrom. aberr. - chrom. analysis B-2773.

Seeds of diploid hulled barley were germinated and then treated

with freshly prepared aqueous solutions of LSD. The seeds were given two treatments of 4 and 8 hours duration in a solution containing 25 μg./ml. of LSD. These treatments were followed by 4 and 8 hour recovery periods, respectively. Observations on various types of chromosomal aberrations were recorded in well spread metaphase cells. There was a significant increase in the mitotic index in both treatments. A significant decrease in seedling height was also found. There were extensive chromosomal aberrations in some cells and fewer in others. Tables are provided. Very few dicentrics could be scored since most of the breaks appeared to be involved in rejoining. It was found that LSD induced chromosome breaks at the primary constriction, the consequence of which was the production of a large number of fragments which appeared to be acentric. Nearly half of the breaks were found to be located in the region of primary constriction. LSD is quite effective in inducing chromosomal aberrations in barley. However, they are qualitatively different from those induced by other mutagenic agents.

135. Kasirsky, G., and Tansy, M. F.
TERATOGENIC EFFECTS OF METHAMPHETAMINE IN MICE AND RABBITS.
Teratology, 4(2): 131-134, 1971.
E - res. pap. - in vivo - tables - mice - rabbits - teratogenicity - exper. admin. - injection - extended use - female consumpt. - dose/response - stage of devel. - congenit. defects - fetal maldevel. B-2774.

Pregnant mice and New Zealand White rabbits were given methamphetamine HCl intravenously during days 9 to 15 and 12 to 30 of gestation, respectively. Within five minutes after injection, they showed excitement which continued for 6 to 7 hours and showed marked reduction in food and water intake for 2 to 3 days. Less than two percent of the offspring of the mice given 5 mg./kg. on days 9 to 15 had anomalies. But when 10 mg./kg. was given on days 9 to 15, a 13.6 percent incidence of anomalies was observed. Offspring of the rabbits receiving 1.5 mg./kg. of methamphetamine on days 12 to 15, 15 to 20, and 12 to 30 of gestation showed an incidence of fetal anomalies of 12, 4, and 15.5 percent, respectively. Principal anomalies were exencephaly, cleft palate, microphthalmia, anophthalmia, and cyclopia. No cardiac anomalies occurred. Offspring sired by treated males showed no significant weight change and had no greater abnormality rate than controls. Dexamphetamine sulfate, an analogue of methamphetamine HCl, has also been reported to be teratogenic.

136. Kato, T., and Jarvik, L. F.
LSD-25 AND GENETIC DAMAGE.
Diseases of the Nervous System, 30: 42-46, 1969.
E - gen. pap. - in vitro - tables - humans - chromosome damage - exper. admin. - intent. use - single dose - female consumpt. - chrom. aberr. - chrom. analysis, peripheral B-2775.

References are given to three reports to date on abnormalities induced in embryos or offspring of animals and in one human who was exposed to LSD in utero. Conflicting reports on the effects of LSD on chromosomes in vitro and in vivo are discussed and data is presented in a table for comparison with new experiments with LSD and other drugs. Values range from 0 to 28 percent incidence of breaks in the controls used in nine studies. Of eight experimental subjects, cells in two did not respond to in vitro addiction of LSD with an increase in breaks. However, an average of 10.2 percent incidence of breaks was induced in the eight compared to 4.7 percent in the controls. Chromosomes of a girl who had taken nine "trips" during the preceding five months showed no damage. Individual differences in response imply caution in evaluating results. It was found that LSD, ergonovine maleate, and aspirin had almost identical breaking effects. Caffeine has also been reported to cause chromosome breaks.

137. Kato, T., Jarvik, L. F., Roizin, L., and Moralishvili, E.
CHROMOSOME STUDIES IN PREGNANT RHESUS MACAQUE GIVEN LSD-25.
Diseases of the Nervous System, 31(4): 245-250, 1970.
E - res. pap. - in vivo - tables - primates - chromosome damage - exper. admin. - s. c. admin. - extended use - female consumpt. - chrom. aberr. - congenit. defects - fetocidal - chrom. analysis, peripheral B-2776.

A preliminary study was undertaken with six pregnant Rhesus monkeys, two of which acted as controls. Peripheral blood was taken before and several times after the subcutaneous administration of a total of .875 to 9 mg./kg. of LSD per experimental animal over a six week period. The minimum doses exceeded the highest doses reportedly taken by man. They were sufficient enough to produce unmistakable behavioral changes such as staring, defensive, and frightened looks. Human leukocyte culture techniques were used. Fifty metaphases from each monkey were examined and it was found that there was a transient increase in chromosome breaks in three of the four experimental monkeys. The highest percentage of breaks was 12 percent which was twice the highest percentage found in the control monkeys. Tables are provided.

Two newborns were stillborn and one died shortly after birth from pneumonia. All three were the offspring of experimental females. The stillborn fetuses showed facial deformities. The fourth experimental infant and one of the control infants showed a high percentage of chromosomal breakage. However, both rates returned to normal. While it was not unusual for large doses of a drug to be teratogenic, it was important to note that the treatment was only started in the later stages of pregnancy.

138. Kruskal, W. H., and Haberman, S.
CHROMOSOMAL EFFECT AND LSD: SAMPLES OF FOUR.
Science, 162(3861): 1508, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - exper. admin. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2777.

This letter is a criticism of the statistical interpretation, the experimental design, and the reporting of Sparkes et al. (Science, 160: 1343, 1968). They examined the chromosomes in the leukocytes from three groups of four subjects, each. These groups of users of LSD, people medically treated with it, and a group of controls. In finding no significant difference, a misimpression was given in that in comparing two samples of only four subjects, the real difference between the groups must be very large to have much probability of detection. Detailed aspects of analysis are considered. It is also noted that the ages in the three groups were not comparable, that it was not stated whether the cells were observed blindly, and that the range of the results from the two testing laboratories was not given.

139. Kumar, S., and Kunwar, K. B.
CHROMOSOME ABNORMALITIES IN CANNABIS ADDICTS.
Journal of the Association of Physicians of India, 19: 193-195, 1971.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - female - consumpt. - male consumpt. - chrom. aberr. - chrom. analysis, bone mar. B-2778.

Chromosomes of seven cannabis addicts who had taken the drug for the past 15 to 20 years regularly were examined by direct bone marrow preparation techniques. The results from these women and men whose ages ranged from 40 to 57 were compared with those of 25 age-matched controls. Chromosome breakage rate in the cannabis addicts was found to be 5 percent of 157 cells analysed, compared to the controls who had a rate of .2 percent in 500 cells scored. There was a significant increase in the number of gaps and

breaks in cannabis addicts. In addition, one cell which showed an endoreduplication, one ring chromosome, and one cell showing a 57, XR, G+ karyotype configuration were observed. The consequences of such aberrations are suggested. Tables and figures are presented.

140. Kushnick, T., Robinson, M., and Tsao, C.
NARCOTIC ADDICTS AND THEIR NEWBORNS.
Journal of the Medical Society of New Jersey, 69(9): 727-728, 1972.
E - gen. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - female consumpt. - male consumpt. - chrom. aberr. - chrom. analysis, peripheral - confound. agent
B-2779.

An experiment was undertaken to determine if there was an increase in the chromosomal breakage rate and a decrease in the mitosis rate in 60 adult narcotic addicts and 18 newborn offspring of addicted mothers. Controls consisted of 31 adults and 15 newborns. Peripheral leukocyte chromosome analysis was undertaken. The chromosomal breakage rate was very significantly increased and the mitosis rate was significantly reduced but this was only found with the adult addicts. No abnormal chromosome configurations were observed. The etiology of the anomalies was not determined. Several studies are cited on the increased chromosomal breakage and the mitotic suppression due to hepatitis.

141. Kushnick, T., Robinson, M., and Tsao, C.
45, X CHROMOSOME ABNORMALITY IN THE OFFSPRING OF A NARCOTIC ADDICT.
American Journal of Diseases of Children, 124: 772-773, 1972.
E - gen. pap. - case rep. - humans - female - chromosome damage - teratogenicity - intent. use - extended use - female consumpt. - chrom. aberr. - congenit. defects - birth, full term - lab. test
B-2780.

During a cytogenetic study of adult narcotic addicts and their newborn offspring, the first child with chromosomal aneuploidy was discovered. The infant, with a 45, X karyotype and physical deformities, was born to a user of heroin and cocaine. The mother had used these drugs for 1 1/2 years and had supposedly ceased usage after the first trimester of pregnancy. Delivery was difficult due to a 60 percent abruptio placenta. The baby developed a respiratory distress syndrome soon after birth but recovered completely 48 hours after birth. Physical examination results as well as those from laboratory tests are given. Genetic abnormality was

found in all 61 cells examined. Sex chromatid pattern was abnormal with male negative findings. Physical abnormalities included an easily palable mass in the right lower quadrant of the abdomen. Slight clitoromegaly was present. The extremities had such abnormalities as a left palmar transverse crease, left cubitus valgus, right fifth finger clinodactyly, and absent fifth toes bilaterally. No history of the father could be obtained.

142. Lawler, H. C.
ACTION OF HALLUCINOGENS AND PHENOTHIAZINES ON EMBRYOLOGICAL DEVELOPMENT.
Federation Proceedings; Federation of American Societies for Experimental Biology, 29(2): 649Abs., 1970.
E - abst. - in vivo - teratogenicity - exper. admin. - single dose - congenit. defects - embryo. maldevel. B-2781.

The hallucinogens mescaline and LSD, and three phenothiazines were added to solutions to test the differences in their effect on three species of sea urchins. Effects were compared when exposed before fertilization and during gastrulation. Mescaline and LSD added during gastrulation reduced the growth of the endoskeleton. Mescaline had the most marked effect on the length of the rods in the ventral arms. Phenothiazines stopped development of the embryo whether they were added during gastrulation or before fertilization. The drugs act during the period of differentiation, but appear to have different mechanisms of action.

143. Leppert, M. F.
CHROMOSOMAL DISORDERS OF THE UNBORN.
Bulletin of the American College of Nurse-Midwifery, 13: 14-17, 1968.

E - gen. pap. - sec. disc. - chromosome damage - teratogenicity - intent. use - chrom. aberr. - congenit. defects - carcinogen. effect - no effect B-2785.

The author gives a short discussion on chromosomal aberrations and their effect on the unborn child. The results of studies with LSD are mentioned. It has been found that LSD causes chromosomal breaks. This is quite serious in that portions of genetic material could be lost and in that the particular cells are able to survive for long periods of time although being abnormal. Since breaks and deletions are found in certain tumor cells and leukemias, there is a possibility that LSD can cause these illnesses. Case reports and animal studies are cited which show that LSD crosses

the placental barrier and can possibly result in congenital malformations.

144. Levick, L. J., and Levick, S. N.
TESTICULAR CHORIOCARCINOMA IN LSD USERS. COINCIDENCE OR CAUSE?
Journal of the American Medical Association, 217(4): 475-476, 1971.
E - gen. pap. - case rep. - humans - chromosome damage - intent. use - extended use - male consumpt. - chrom. aberr. - carcinogen. effect B-2782.

The author presents two case reports of young men who had experienced 20 to 30 LSD trips and who were found to have testicular choriocarcinoma. Both men experienced swelling of the testicle and underwent chemotherapy. Surgery was performed on one subject and three tumor containing nodals were found. Choriocarcinoma of the testicle is a rare malignant tumor which makes up only one percent of all testicular tumors diagnosed. The author cites a few references concerning the teratogenic effect of LSD, on its chromosome breakage effect, and on the possibility of it being carcinogenic. There could possibly be a relationship between the use of LSD and choriocarcinoma of the testes.

145. Long, S. Y.
DOES LSD INDUCE CHROMOSOMAL DAMAGE AND MALFORMATIONS? A REVIEW OF THE LITERATURE.
Teratology, 6(1): 75-90, 1972.
E - gen. pap. - review - tables - hamsters - humans - mammals - primates - chromosome damage - teratogenicity - exper. admin. - intent. use - therapeut. use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - no effect - chrom. analysis, peripheral - chrom. analysis, bone mar. B-2783.

The author presents a review of the literature on the effects of LSD on chromosomal damage and malformations. Papers examined consist of in vitro studies, in vivo studies, studies of LSD on meiotic chromosomes, cytogenetic studies on children whose parents had used LSD, and studies on the relationship between LSD and chromosomal breakage and leukemia. Tables are provided which compare the results of the studies reviewed. When LSD was added to cell cultures in vitro at .01 to 10 μg./ml., breaks were found in the leukocytes of humans, monkeys, and rat kangaroos. In contrast, other reports showed no increase in breaks at .4 to 45 μg./ml. of LSD when added to hamster embryo cells, hamster lung cells, and

human lymphocytes. Of 161 LSD users, 53 percent had chromosomal break frequencies which exceeded the control range. The same was true of 30 percent of 37 patients treated with LSD. However, there was no relationship between the number of breaks and the total amount, the number of doses, and the time between the last dose of LSD and blood sampling. The drawbacks of in vitro chromosomal analysis are discussed. There was no increase in the frequency of chromosomal abnormalities found in studies conducted on male meiosis. Of the 78 children and one abortus who were exposed to LSD in utero, 17 children and the abortus were found to have an increase in the number of breaks. The breaks were transitory in nature. Concerning the teratogenic effect of LSD, 161 children were examined, and 7 were found to have familial defects and 16 had sporadic congenital disorders. LSD does increase chromosome breakage in vitro, however, cultured leukocytes from LSD users, from patients treated with LSD, and from children exposed to LSD in utero show little chromosomal breakage.

146. Loughman, W. D., Sargent, T. W., Israelstam, D. M.
LEUKOCYTES OF HUMANS EXPOSED TO LYSERGIC ACID DIETHYLAMIDE: LACK OF CHROMOSOMAL DAMAGE.
Science, 158(3800): 508-510, 1967.
E - gen. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - female - consumpt. - male consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2784.

Leukocytes from eight humans who had had recent exposure to large doses of LSD (one took 4,000 μg. the day before sampling) were examined for chromosome abnormalities. The number of abnormalities was not signigicantly greater than that in the control cultures. The technique for culturing was similar to that of Cohen et al. who have reported chromosomal damage by LSD added in vitro, and in one user. In addition, the rate of aberrations in control cultures was much lower than his, but in agreement with others. Reasons for the differences in results are analysed. Studies on the clearance of LSD (which is most actively concentrated in the liver), and the relation of dose to concentration in the blood are discussed. The lack of significant effect on chromosomes is in agreement with expectation based on these reports.

147. Loughman, W. D., and Sargent, T. W.
CHROMOSOME DAMAGE BY LSD.
Science, 159: 1492-1493, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - intent. use - chrom. aberr. - no effect B-2786.

This letter was written in response to another letter which conveyed the comment that with different statistical techniques, the present authors could have shown a significant increase in chromosomal damage in LSD users used as subjects in a previous experiment. The present writers discuss the statistical techniques used and the results found in their previous experiment. Significant results were found in parts of the data but it was felt that some of the variances could have been due to chance. They realized that there was some support for the contention that LSD does cause some chromosomal damage. However, from the data, the support for such a conclusion was not strong. From the scores of several different statistical techniques, it was felt that the cause and effect relationship between LSD and chromosomal aberrations could not be expressed with any reliability. The authors feel that the previous writers did show statistical results that were significant by pointing to differences which are the result of random sampling error.

148. Louria, D. B.
LYSERGIC ACID DIETHYLAMIDE.
New England Journal of Medicine, 278(8): 435-438, 1968.
E - gen. pap. - review - sec. disc. - humans - mice - rats - chromosome damage - exper. admin. - intent. use - chrom. aberr. - no effect B-2787.

The author presents a short review of the literature dealing with the pharmacology, medical uses, and the dangers of LSD. Dealing with chromosomal changes, the author cites a few of the early studies that were done. The findings were that 1 to 10 mμg./ml. of LSD was enough to cause chromosomal damage in human leukocytes. In addition, two of three studies of leukocytes of LSD users showed about 80 percent of the users with increases in chromosomal breakage. Infants of mothers who took LSD during the early months of pregnancy also showed an increase in the number of chromosomal breaks. The findings with humans have been supported by research done with pregnant mice and rats in which high rates of embryological abnormality and stillbirths were recorded in the offspring and embryos of females who had been administered LSD. The author feels that chromosomal studies on reproductive tissues and extensive epidemiologic studies must be undertaken. The possibility of induced neoplastic changes in LSD users and genetic abnormalities in the offspring of users is great.

149. Lucas, G. J., and Lehrnbecher, W.
EVALUATION OF CHROMOSOMAL CHANGES.
New England Journal of Medicine, 281: 1018, 1969.

E - lett. ed. - gen. disc. - humans - chromosome damage - intent. use - oral admin. - chrom. aberr. - no effect - hypothesis B-2788.

The writer states in this letter that there are a few studies which have shown that LSD causes chromosomal damage while other studies have shown no chromosomal aberrations. There seems to be more support that LSD has an effect of suppressing cell mitosis. The writer found that there were few chromosomal anomalies in 20 patients who had ingested LSD. He comments on and discusses the radioautographic methods used in the investigation of LSD and chromosomal damage. The small amount of experimental data seems to suggest a direct interaction, probably by intercalation with the DNA helix, causing confirmational changes. The writer feels that a more thorough understanding of the relationship between LSD and its possible effects must be understood before a cause and effect association can be firmly stated.

150. Lucas, G. J., and Lehrnbecher, W.
CHROMOSOMAL EFFECTS OF LSD-25, A CONTROVERSY?
Journal of the Arkansas Medical Society, 66(10): 348-349, 1970.
E - res. pap. - in vivo - humans - chromosome damage - intent. use - chrom. aberr. - no effect - chrom. analysis B-2789.

An in vivo experiment was done with the lymphocytes of 20 undescribed patients who had been exposed to LSD. Cultures were prepared, incubated for 72 hours, and analysed. Twenty metaphase spreads for each of 20 control individuals were examined and only one chromatid break was found. With the experimental group, 5 individuals did not show any chromatid breaks while 14 patients showed from 1 to 3 breaks in some cells. The conclusion was that LSD did not increase the breakage rate significantly. Results of other studies are discussed and possible explanations for the conflicting evidence are given.

151. Mabuchi, T., and Arnason, T. J.
ABSENCE OF CHLOROPHYLL MUTATIONS IN ARABIDOPSIS TREATED WITH LSD.
Arabidopsis Information Service, No. 6: 27, 1969.
E - abst. - in vivo - tables - plants - chromosome damage - exper. admin. - chrom. aberr. - no effect - chrom. analysis B-2790.

Experiments are described in which batches of seeds of Arabidopsis thaliana were soaked in LSD solution at concentrations of either 1, 10, and 100 μg./ml. for 24 hours or in 1, 10, and 50 μg./ml. of

LSD for 17 hours followed by a second soaking in concentrations of .5, 5, and 25 μg./ml. of LSD for an additional 8 hours. Comparative treatments with one percent ethyl methanesulfonate and another with 10 kR. of X-rays were provided. A table is provided with the mutation frequencies found in the seeds treated with LSD, ethyl methanesulfonate, and X-rays. No mutations appeared in the progenies of the 165 LSD treated plants. Mutations were found with the two other treatments. LSD did not show any mutagenic effects.

152. Malleson, N.
L. S. D. AND CHROMOSOMES.
British Medical Journal, 2: 121, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - chrom. aberr. - no effect B-2791.

The writer of this letter comments on the opening passage of an editorial (Brit. Med. J., 1: 778, 1968) on the genetic effects of LSD. The writer suggests that all drugs should be tested to see whether they might cause genetic damage rather than just those that might provide "kicks" for their users. To suggest that LSD was genetically harmful could possibly act as a deterrent to potential users. However, this action would greatly impede clinical studies with LSD related to the treatment of neuroses and other psychiatric conditions. There have not been numerous case reports of genetically deformed babies born in large cities having large hippy populations which abuse LSD quite heavily. The warning was given that LSD should not be used during pregnancy, but this is a sensible precaution for all drugs. There is little evidence that LSD should be discontinued in the therapeutic areas of research.

153. Markowitz, E. H., Brosseau, G. E., Jr., and Markowitz, E.
GENETIC EFFECTS OF LSD TREATMENT ON THE POST-MEIOTIC STAGES OF SPERMATOGENESIS IN DROSOPHILA MELANOGASTER.
Mutation Research, 8(2): 337-342, 1969.
E - res. pap. - in vivo - tables - fruit flies - chromosome damage - exper. admin. - oral admin. - extended use - male consumpt. - chrom. aberr. - spermatogen. effect - chrom. analysis B-2792.

An in vivo experiment was carried out in which fruit flies were given .1, 5, or 10 mg./ml. of LSD to feed upon. Chromosomes of their progeny were examined for rearrangements which would give evidence of chromosomal breakage and for sex-linked recessive lethal mutations. It could easily be established which were the

LSD fed flies as they tended to be lethargic and quiescent. Chromosomal rearrangements were assayed by the transvection method. The heritable rearrangements of the LSD treated males could not be found in their progeny. From this, there was no support that LSD caused any chromosome breakage. However, it was found that both the higher treatment groups showed significant increases in sex-linked recessive lethal mutations. The researchers compiled a table giving the results of all the studies undertaken on the effect of LSD on the frequency of recessive lethal mutations in the post-meiotic stages of spermatogenesis. It was found that only LSD concentrations of at least 2 mg./ml. gave significant increases in mutation rates over the controls. The data suggest that this may be the threshold of response and, also, that there is no increase in the frequency of mutations with increases in doses. The effective dose for the fruit fly is much higher that that found in human users or tissue cultures. The physiological differences between humans and fruit flies which might account for this difference are discussed. LSD, in high concentrations, is a weak mutagen and a relatively ineffective chromosome breaking agent in the fruit fly.

154. Markowitz, E., and Klotz, J. H.
LSD AND CHROMOSOMES.
Journal of the American Medical Association, 211(10): 1699, 1970.
E - lett. ed. - gen. disc. - humans - chromosome damage - chrom. aberr. B-2793.

The writers did their own statistical analysis on the results found by Tjio, et al. in their study (J. A. M. A., 210: 849, 1969) on the effects of LSD on human chromosomes in vivo. The researchers measured the chromosome aberration rates in the subjects before and after the administration of LSD and found no significant differences. The present writers concluded that LSD had a significant effect on both dosage groups used when more powerful statistical methods were used. The results of the previous experiment are outlined and the statistical methods used by the writers are described. It was felt that the previous analysis was invalid in that it should have been based on the negative hypergeometric distribution rather than on the positive hypergeometric distribution of the data. The chromosome aberration rates in lymphocytes of some humans increase significantly after treatment with LSD.

155. Martin, P. A.
CANNABIS AND CHROMOSOMES.
Lancet, 1: 370, 1969.
E - lett. ed. - in vivo - in vitro - rats - chromosome damage -

exper. admin. - i.p. admin. - extended use - birth, pre term. - chrom. analysis B-2794.

The writer discusses three experiments which were carried out. Cultured rat leukocytes were prepared, incubated, and treated in the usual manner. A homogeneous emulsion of cannabis resin in concentrations of 40, 60, 100, and 200 μg./ml. of culture medium were added to different rat specimens for exposure periods of 6, 24, 48, and 72 hours. In the second experiment, cells of 15 to 16 day old rat embryos were grown from 4 to 7 days. When fibroblasts were noted, cells were subcultured in different concentrations of cannabis resin which were added 6 hours later. The cells were exposed for 24 hours. The concentrations were 100 and 200 μg./ml. In the third experiment, 15 pregnant rats were injected intraperitoneally with 4.2 mg./kg. of cannabis resin daily on days 1 to 6 of gestation and were sacrificed on days 11 to 13. Embryos were removed and homogenized by pipetting and then incubated in medium. The cells were grown from 3 to 6 days and then processed for chromosomes. The only chromosomal abnormalities found in the three experiments were chromatid gaps and their incidence was no greater than in the controls. The only effect found was that at the higher concentrations there was mitotic inhibition.

156. Matera, R. F., Zabala, H., and Jimenez, A. P.
BIFID EXENCEPHALIA. TERATOGEN ACTION OF AMPHETAMINE.
International Surgery, 50(1): 79-85, 1968.
E - gen. pap. - case rep. - humans - male - teratogenicity - intent. use - congenit. defects - death - fetal maldevel. - autop. B-2795.

A case report is provided of a male newborn who had two oviform prominences, 10 cm. high, on the upper part of his head. The mother had been taking dextroamphetamine before conception, had stopped taking it when she found that she was pregnant, but resumed its use five weeks after conception. The dosage taken was 20 to 30 mg. per day and was continued during the rest of the pregnancy. X-rays showed that part of the frontal bones of the skull, along with the occipital bone and part of the parietals, were ossified. The frontal and occipital bones ended abruptly leaving a large open upper space with two masses of soft tissue protruding. It appeared as if the posterosuperior part of the frontal lobe seemed to be folded down and forward. In the posterior fossa, the cerebellum showed a normal position, size, and shape. Closer observations are given in more detail. An operation was tried, to

free the whole meningeal sac. Four hours after the operation, the child suffered a respiratory arrest, and died. Biopsy results are provided. The author discusses the toxicity of amphetamine along with the pharmaco-dynamic action of the drug. He concludes that it must have a teratogenic effect, especially when taken during the full embryogenic period.

157. Maugh, T. H., III.
LSD AND THE DRUG CULTURE: NEW EVIDENCE OF HAZARD.
Science, 179: 1221-1222, 1973.
E - gen. pap. - gen. disc. - humans - teratogenicity - intent. use - congenit. defects - no effect - birth, full term B-2796.

The author gives a short discussion and a review of the literature on the effect of LSD on genetic defects. Many studies have shown that LSD has a detrimental effect, and yet, an equally large number of studies have shown that there are no such effects. The complications of using the in vivo techniques are mentioned and it is suggested that chromosomal damage in cultured cells could be due to an artifact of the technique used in that type of study. The difficulty in determining if LSD is teratogenic in humans is also discussed. The author goes on to discuss the results of an experiment carried out by Jacobsen, G. B., and Berlin, C. M. (J. A. M. A., 222: 1367, 1972) in which 10 percent of the newborns of LSD using parents were found to have incidence of chromosomal breakage than normal. Of all the pregnant women enrolled in the study during the first three months of pregnancy, 43 percent had spontaneous abortions. Fourteen embryos which were intact enough for analysis, were examined and it was found that 4 showed gross abnormalities. Due to the physiological and social conditions surrounding these subjects, the least that could be concluded was that multiple drug use and the counter-culture environment present a very severe hazard to birth. The article is finished by a discussion of a report that suggests that increased susceptibility to disease may result, at least in part, from LSD use.

158. McGlothlin, W. H., Sparkes, R. S., and Arnold, D. O.
EFFECT OF LSD ON HUMAN PREGNANCY.
Journal of the American Medical Association, 212(9): 1483-1487, 1970.

E - res. pap. - tables - humans - teratogenicity - therapeut. use - oral admin. - abort. rate - congenit. defects - no effect B-0622.

The authors studied the outcome of 148 pregnancies following

parental, therapeutic ingestion of LSD. Data related to pregnancies and LSD use was obtained for both parents. The number of medical LSD exposures was small in that 47 percent of the pregnancies involved only a single administration to just one parent. The range of combined exposures for both parents was 1 to 85. The median single dose was 125 μg. The median medical and illicit exposure for both parents in this study was 25. The spontaneous abortion rate in the group limited to the therapeutic administration of LSD fell within the normal frequencies. The rate for those who had taken illicit LSD was considerably higher, but one woman accounted for five of the ten abortions recorded. More abortions were found when the mother only received the drug than when the father only received it. The percentage of live births which were premature was found to be within the normal range. Of the 120 live births, 14 were found to have congenital anomalies including minor anomalies not considered significant. The only indication provided by this experiment was that the use of LSD prior to conception by women may increase the incidence of spontaneous abortion, although no clearcut causal relationship could be found.

159. Muñoz, E. R., and Barnett, B. M.
SEX-LINKED RECESSIVE LETHAL TEST WITH LSD IN DROSOPHILA MELANOGASTER SPERM.
Drosophila Information Service, 44: 54, 1969.
E - abst. - in vivo - tables - fruit flies - chromosome damage - exper. admin. - injection - stage of devel. - chrom. aberr. - spermatogen. effect B-2797.

Experiments were undertaken to test recessive and dominant lethality and translocation frequency in different stages of gametogenesis. Male fruit flies were intraabdominally injected with .1 mg./ml. of solution of LSD and mated with virgin females. Half of the males were mated immediately after the treatment and the other half 24 hours later. Standard recessive lethal tests were performed with the F1 females. The results are provided in a table. It was found that there was an increase in the frequency of mutations in the progeny of the males mated immediately after treatment. However, there was no increase in the frequencies found in the progeny of the males mated 24 hours after treatment. The reason for this difference could possibly be a differential sensitivity to the drug since in the first instance, a larger proportion of cells treated as mature sperm were recovered.

160. Myers, W. A.
LSD AND MARIHUANA - WHERE ARE THE ANSWERS?
Science, 160: 1062, 1968.
E - lett. ed. - gen. disc. - humans - mammals - chromosome damage - teratogenicity - chrom. aberr. - congenit. defects - no effect - chrom. analysis, peripheral B-2798.

There is only a small amount of evidence regarding the harmful effects of LSD and what there is, is controversial. Two studies are cited which show that LSD induced an abnormally high rate of chromosomal damage and one study is cited which fails to find any effect and which raises important methodological problems related to this type of research. Damage to peripheral blood cells is not sufficient enough to conclude that LSD is a genetic risk. It is not even known if LSD penetrates gonadal tissue. Teratogenic effects of LSD are another separate area of investigation since the mechanism for this action is likely not to be genetic in nature.

161. Naeye, R. L., Blanc, W., and LeBlanc, W.
POSTMORTEM FINDINGS IN OFFSPRING OF HEROIN ADDICTS.
Laboratory Investigation, 28(3): 392-393, 1973.
E - abst. - res. pap. - in vivo - humans - teratogenicity - intent. use - female consumpt. - chrom. aberr. - placent. funct. - no effect - autop. - birth, full term B-2799.

The autopsy material from 29 newborns whose mothers had used heroin up to delivery, 10 newborns who were exposed to heroin only during early pregnancy, 3 newborns whose mothers had been on methadone, and a newborn control group was analysed. The incidence of hyaline membrane disease in the infants of the various groups was 40 percent, 0 percent, 67 percent, and 57 percent, respectively. It was concluded from the study that there was no specific disease process or fetal abnormality that could be directly related to heroin. However, the excessive prematurity and perinatal deaths in the offspring of addicts appear to be related to the amniotic fluid infection syndrome.

162. Nair, V., Bau, D., and Siegel, S.
EFFECT OF LSD IN PREGNANCY ON THE BIOCHEMICAL DEVELOPMENT OF BRAIN AND LIVER IN THE OFFSPRING.
Pharmacologist, 12(2): 296, 1970.
E - abst. - in vivo - rats - teratogenicity - exper. admin. - oral admin. - extended use - congenit. defects - no effect - autop. - birth, full term B-2800.

The effect of feeding rats LSD on different days of gestation on the development of 5-hydroxytryptamine (5HT) and norepinephrine (NE) in the brain and of hexobarbital oxidase (HO) and 0-demethylase (OD) in the liver of their offspring was tested in some on postnatal day 40 and in the others on day 80. Significant lowering of brain 5HT was noted in the groups exposed to 100 μg. of LSD on gestation days 1 to 3, 9 to 12, 13 to 15, or 18 to 21. There were no significant changes in the brain NE. The HO and OD liver enzymes were suppressed in the female offspring from exposure days 1 to 3 and stimulated in the male offspring from exposure days 13 to 15. No gross organ malformations were noted.

163. Neu, R. L., Powers, H. O., King, S., and Gardner, L. I.
CANNABIS AND CHROMOSOMES.
Lancet, 1: 675, 1969.
E - lett. ed. - in vitro - humans - chromosome damage - exper. admin. - chrom. aberr. - no effect - chrom. analysis B-2801.

Studies are described which were carried out to determine the possible effects of Δ^8-tetrahydrocannabinol (Δ^8-THC) on human leucocytes in vitro. Δ^8-THC was added during the last 24 hours of the culturing period making final concentrations of 20, 30, 35, and 40 μg./ml. It was found that fewer metaphases were available for analysis in the cultures with the higher concentrations because of a decreased mitotic index. No more than 5 percent of the metaphases in the control and experimental cultures had gaps or breaks. In addition, no structural changes other than the few gaps and breaks were found.

164. Neu, R. L., Powers, H. O., King, S., and Gardner, L. I.
Δ8- AND Δ9-TETRAHYDROCANNABINOL: EFFECTS ON CULTURED HUMAN LEUCOCYTES.
Journal of Clinical Pharmacology and New Drugs, 10: 228-230, 1970.
E - gen. pap. - in vitro - humans - chromosome damage - exper. admin. - single dose - chrom. aberr. - no effect - chrom. analysis, peripheral B-2802.

An experiment was carried out to determine if Δ^8- and Δ^9- tetrahydrocannabinol cause similar chromosomal aberrations when added to human blood cultures. Δ^8-THC was added to the cultures at concentrations of 30, 35, 40, and 45 μg./ml. 24 hours prior to the harvesting of the cells. Alcohol was added to the whole blood cultures at a concentration of .01 ml./ml. The mitotic index decreased but was never below 2.7 percent with the alcohol. Less

than 30 metaphases were available for analysis in cultures with concentrations of 50 μg. /ml. or more because of a lower mitotic index and the poorer quality of metaphases. No more than 5 percent of the metaphases in the experimental and the control cultures had gaps or breaks. No structural changes other than these were observed. In preliminary experiments, Δ^9-THC had shown similar findings.

165. Neuberg, R.
DRUG DEPENDENCE AND PREGNANCY: A REVIEW OF THE PROBLEMS AND THEIR MANAGEMENT.
Journal of Obstetrics and Gynaecology of the British Commonwealth, 77: 1117-1122, 1970.
E - gen. pap. - gen. disc. - humans - teratogenicity - intent. use - female consumpt. - male consumpt. - abort. rate - spermatogen. effect - no effect B-1080.

The author discusses the use of heroin, amphetamine, LSD, marijuana, and barbiturates in the woman during pregnancy and their consequences. In one experiment cited, it was found that out of 77 pregnancies with heroin addicts, there were 37 abortions of which 14 were criminally induced. In another study, the cases of 66 pregnant narcotic addicts were analysed and it was found that 41 percent showed obstetric complications. There was a total of 57 full term births, 13 premature deliveries, and 5 stillbirths. With narcotic addicts, it is difficult to know whether the complications are due to the heroin alone, or to the lack of antenatal care or the degree of physical deterioration, malnutrition, and ill health. Maternal withdrawal and neonatal withdrawal symptoms are discussed. Amphetamine does not cause congenital deformities but there is some evidence of neonatal withdrawal symptoms. Reports and experiments on the effects of LSD are given and the contradictory results shown. It is felt that spontaneous abortion occurs most frequently with women who have taken LSD either before or during pregnancy. There is a high incidence of abnormalities in aborted fetuses and fetal abnormalities have also been reported when only the father has taken the drug. This could possibly be due to a chromosomal defect in the fertilizing sperm. There are no accounts of any complications in pregnancy due to either cannabis or barbiturate abuse.

166. Neuberg, R.
DRUG ADDICTION IN PREGNANCY. REVIEW OF THE PROBLEM.
Proceedings of the Royal Society of Medicine, 65(10): 867, 1972.

E - gen. pap. - gen. disc. - humans - teratogenicity - intent. use - congenit. defects - no effect B-2803.

The drug-dependent pregnant woman is no longer a rarity in obstetric practice. It has been found in most cases that antenatal care is virtually absent. The doctor must be alert to the possibility of neonatal withdrawal problems which, if not recognized immediately, could lead to fatal results. There is no evidence yet, of chromosomal aberrations in newborns of mothers who have taken only pure LSD during early pregnancy. There are several reports which show abnormalities among babies of illicit LSD users. On the basis of present knowledge, serious consideration should be given to the termination of pregnancy when a patient has taken illicit LSD in early pregnancy. The baby is the only easily curable addict since the psychological component of addiction is not present. Whenever possible, they should be placed in care for their own protection.

167. Neuhäuser, G.
CHROMOSOMENVERÄNDERUNGEN DURCH MEDIKAMENTE.
[Drug-induced chromosome aberrations.]
Hippokrates, 41: 396-398, 1970.
G - gen. pap. - review - humans - mice - chromosome damage - exper. admin. - therapeut. use - chrom. aberr. - no effect B-2804.

A review of the literature is presented of the experiments dealing with the mutagenic effects of various chemicals. Chromosome damage was noted in subjects who had been given myleran and also endoxan. There is great controversy over the effects of LSD. The author cites articles by previous investigators who were able to confirm LSD as causing chromosome aberrations, but also notes that others were unable to agree. He suggests further investigation into the precise mechanisms of action of the drug in order to determine its mutagenic potential.

168. Nichols, W. W.
GENETIC HAZARDS OF DRUGS OF ABUSE.
In: Zarafenetis, C. J. D., ed., Drug Abuse: Proceedings of the International Conference. Philadelphia, Pennsylvania: Lea & Febiger, pp. 93-100, 1972.
E - book - gen. disc. - sec. disc. - chromosome damage - intent. use - therapeut. use - chrom. aberr. - no effect B-2805.

The author discusses the genetic danger of mutagenic agents under the headings: "Types of Genetic Damage", "Significance of Induced

Genetic Changes", "Testing for Genetic Damage", and "Assessing Drugs of Abuse". Figures of examples of chromosomal breakages, rearrangements, and of other abnormalities are provided. Methods of testing for genetic damage include cytogenetic methods, host-mediated assay, dominant lethal test, and population monitoring. The contradictory results which have been obtained with LSD would seem to be the result of the populations studied. Drug users are often malnourished, and have a high incidence of hepatitis and virus infection. They may use different drugs, the dosage and purity of which are unknown. The difference in the results of the two best studies on LSD made under medical supervision could possibly be due to the different experimental designs. There are commonly used drugs which have been shown to have chromosome damaging effects which are not ambiguous or confusing.

169. Nielsen, J., Friedrich, U., and Tsuboi, T.
CHROMOSOME ABNORMALITIES AND PSYCHOTROPIC DRUGS.
Nature, 218(5140): 488-489, 1968.
E - gen. pap. - in vivo - tables - humans - chromosome damage - therapeut. use - chrom. aberr. - no effect - chrom. analysis
B-2806.

The frequency of both gaps and breaks was significantly higher in chromosomes of 17 psychiatric patients treated with psychotropic drugs other than LSD than in 13 other patients. There was a significant increase in gaps, but not in breaks, in chromosomes of patients receiving the drugs compared to ten staff members. This indicated that some psychotropic drugs may induce as many gaps and breaks as does LSD. However, five LSD treated patients showed a higher percentage of hyperdiploid cells. No correlation between specific drugs (except LSD) and effects was evident. Testing of new drugs for their damaging effects on chromosomes is advised.

170. Nielsen, J., Friedrich, U., and Tsuboi, T.
KROMOSOMABNORMITETER OG PSYKOFARMAKA. [Chromosome abnormalities and psychotropic drugs.]
Ugeskrift For Laeger, 130: 1527-1528, 1968.
Da - gen. pap. - in vivo - tables - humans - chromosome damage - therapeut. use - chrom. aberr. - no effect - chrom. analysis
B-2807.

The frequency of both gaps and breaks was significantly higher in chromosomes of 17 psychiatric patients treated with psychotropic drugs other than LSD than in 13 other patients. There was a

significant increase in gaps, but not in breaks, in chromosomes of patients receiving the drugs compared to ten staff members. This indicated that some psychotropic drugs may induce as many gaps and breaks as does LSD. However, five LSD treated patients showed a higher percentage of hyperdiploid cells. No correlation between specific drugs (except LSD) and effects was evident. Testing of new drugs for their damaging effects on chromosomes is advised.

171. Nielsen, J., Friedrich, U., Jacobsen, E., and Tsuboi, T.
LSD-BIVIRKNINGER OG -KOMPLIKATIONER. [Side-effects and complications of LSD.]
Ugeskrift For Laeger, 130(34): 1381-1384, 1968.
Da - res. pap. - in vivo - humans - chromosome damage - therapeut. use - female consumpt. - male consumpt. - chrom. aberr. - chrom. analysis, peripheral B-2808.

Five patients, ages 29 to 48 years, who had therapeutically received a total of 2,200 to 17,500 μg. of LSD, the highest single doses varying from 50 to 300 μg., were studied 6 to 38 months after their last treatments for chromosomal damage in the leukocytes. None had been exposed to radiation. An increased frequency of gaps, breaks, and hyperdiploid cells was found when compared with 40 controls; 30 of these being patients in the psychiatric hospital and who had taken large amounts of other psychotropic drugs. Age did not seem to be a factor. The significance of the observation of two cells with endoreduplication and one ring chromosome, in the LSD group, is discussed in relation to cancer and inheritance risks as indicated by other papers cited. However, endoreduplication has been found in healthy humans. Many ring chromosomes were reported in the Hiroshima survivors. Tests on the effects on chromosomes are urged for any new drug.

172. Nielsen, J., Friedrich, U., Jacobsen, E., and Tsuboi, T.
LYSERGIDE AND CHROMOSOME ABNORMALITIES.
British Medical Journal, 2(5608): 801-803, 1968.
E - res. pap. - in vivo - humans - chromosome damage - therapeut. use - female consumpt. - male consumpt. - chrom. aberr. - chrom. analysis, peripheral B-2809.

Five patients, ages 29 to 48 years, who had therapuetically received a total of 2,200 to 17,500 μg. of LSD, the highest single doses varying from 50 to 300 μg. were studied 6 to 38 months after their last treatments for chromosomal damage in the leukocytes. None had been exposed to radiation. An increased frequency

of gaps, breaks, and hyperdiploid cells was found when compared with 40 controls; 30 of these being patients in the psychiatric hospital and who had taken large amounts of other psychotropic drugs. Age did not seem to be a factor. The significance of the observation of two cells with endoreduplication and one ring chromosome, in the LSD group, is discussed in relation to cancer and inheritance risks as indicated by other papers cited. However, endoreduplication has been found in healthy humans. Many ring chromosomes were reported in the Hiroshima survivors. Tests on the effects on chromosomes are urged for any new drug.

173. Nielsen, J., Friedrich, U., and Tsuboi, T.
CHROMOSOME ABNORMALITIES IN PATIENTS TREATED WITH CHLORPROMAZINE, PERPHENAZINE, AND LYSERGIDE.
British Medical Journal, 3(5671): 634-636, 1969.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - therapeut. use - chrom. aberr. - chrom. analysis
B-2810.

Chromosomes were studied in leukocytes of 13 patients treated with chlorpromazine only, 15 treated with perphenazine (usually with orphenadrine, a non-psychotropic anti-Parkinsonian drug), 9 previously treated with lysergide, and also 10 who had taken LSD for psychedelic purposes. A significantly higher frequency of gaps, breaks, and hypodiploid cells was found, and to about the same degree, in those treated with perphenazine and lysergide compared to the 41 controls. Chlorpromazine had a less damaging effect. In those under the age of 50 years treated with perphenazine, there was a correlation between length of treatment, the total amount of drug given, and the frequency of gaps. This did not apply to chlorpromazine. References are cited of studies suggesting that chromosome abnormalities may predispose persons to malignant disorders and to teratogenic effects. It is suggested that drugs inducing major chromosome abnormalities should be used with caution.

174. Nora, J. J., Trasler, D. G., and Fraser, F. C.
MALFORMATIONS IN MICE INDUCED BY DEXAMPHETAMINE SULPHATE.
Lancet, II(7420): 1021-1022, 1965.
E - lett. ed. - in vivo - tables - mice - exper. admin. - i. p. admin. - female consumpt. - congenit. defects - fetal maldevel. - resorpt. rate - no effect - birth, pre term. B-2811.

An experiment was done to determine the effect of dexamphetamine sulphate exposure in utero on the hearts of unborn mice. The drug

was intraperitoneally administered in a dose of 50 μg./gm. to 21 female mice on the 8th day of gestation. The fetuses, removed one or two days before term, were examined under a dissecting microscope, and microscopic serial sections of the thorax were prepared. The resorption rates for the experimental and control groups were 29 percent and 8 percent, respectively. Twelve percent of the 108 fetuses studied in the experimental group showed cardiac malformations such as ventricular septal defects, atrial septal defects, coarctation of the aorta, and right aortic arch. No significant cardiac anomalies were discovered in the 58 control fetuses examined. Eye abnormalities were found in 11 percent of the experimental animals and 3 percent in the controls. Skeletal and other anomalies including cleft lip were found. In the two groups, 38 percent of the experimental fetuses were found to have some type of malformations compared to seven percent in the controls.

175. Nora, J. J., McNamara, D. G., and Fraser, F. C.
DEXAMPHETAMINE SULPHATE AND HUMAN MALFORMATIONS.
Lancet, 1(7489): 570-571, 1967.
E - lett. ed. - in vivo - humans - teratogenicity - therapeut. use - female consumpt. - congenit. defects - no effect - birth, full term
B-2812.

Questionnaires were filled out which reported any prenatal factors, including the use of dexamphetamine sulphate, connected with the births of 219 children under the age of two years who were found to have congenital heart defects. Pregnancy histories were also obtained for a group of control mothers. Information was often supported by correspondence with the referring doctors. The retrospective data showed no causal association between the use of dexamphetamine during pregnancy and congenital heart defects in the infants. A prospective study was done with 52 mothers who had reported the use of dexamphetamine during the critical period of cardiac development. They were compared with 50 mothers who had not used dexamphetamine. The number of children found with congenital anomalies was 9 and 7 in the respective groups. No relation between maternal use of dexamphetamine sulphate and occurrence of congenital heart defects was found.

176. Nora, J. J., Sommerville, R. J., and Fraser, F. C.
HOMOLOGIES FOR CONGENITAL HEART DISEASES: MURINE MODELS, INFLUENCED BY DEXTROAMPHETAMINE.
Teratology, 1: 413-416, 1968.
E - gen. pap. - in vivo - mice - teratogenicity - exper. admin. -

i. p. admin. - single dose - female consumpt. - congenit. defects - birth, pre term. - hypothesis B-2813.

On the eighth day of gestation, females of two strains (A/J and C57BL/6J) of mice were given a single intraperitoneal injection of 50 μg. /gm. of dextroamphetamine sulfate. Two corresponding control groups were used. Fetuses were removed one or two days before term, examined under the dissecting microscope, and serial sections of the thorax were prepared. The A/J control fetuses had more spontaneous malformations and cardiac anomalies than did the C57BL/6J control fetuses. It was found that there was a significant increase in the total malformations and in the cardiovascular anomalies in both strains of mice following maternal administration of dextroamphetamine sulfate. There was a significant excess of atrial septal defects in the A/J mice and of ventricular septal defects in the other strain of mice. It is hypothesized that the administration of this drug increases the frequency of the type of cardiac malformation that tends to occur spontaneously in each of the strains of mice.

177. Nora, J. J., and Vargo, T. A.
CONGENITAL MALFORMATIONS IN FOUR ANIMAL SPECIES FOLLOWING MATERNAL EXPOSURE TO DEXTROAMPHETAMINE.
Southern Medical Journal, 62: 1550, 1969.
E - abst. - in vivo - fruit flies - humans - mice - mammals - teratogenicity - exper. admin. - therapeut. use - female consumpt. - congenit. defects - no effect B-2814.

Continuing research has been carried out to determine the teratogenic effects of dextroamphetamine sulphate. It was found that there was a significant difference in total malformations and cardiac malformations between the fetuses of dextroamphetamine treated and control animals in two strains of mice. Malformations were increased significantly in fruit flies but not significantly in white leghorn chicks. A retrospective study of humans in the years 1962 to 1966 failed to distinguish infants with and without congenital defects on the basis of the use of dextroamphetamine by their mothers. However, in a study done between 1966 and 1969, a significant difference was found between the two groups of subjects, similar to the two groups in the previous experiment.

178. Nora, J. J., Vargo, T. A., Nora, A. H., Love, K. E., and McNamara, D. G.
DEXAMPHETAMINE: A POSSIBLE ENVIRONMENTAL TRIGGER IN CARDIOVASCULAR MALFORMATIONS.
Lancet, 1(7659): 1290-1291, 1970.
E - lett. ed. - in vivo - humans - teratogenicity - therapeut. use - female consumpt. - congenit. defects - no effect - birth, full term B-2815.

The writers give their previous results that dexamphetamine sulphate causes congenital cardiovascular malformations in two strains of mice, in fruit flies but not in white leghorn chicks or in humans. However, in reviewing the data on their continuing investigation, they found a significant relationship between the use of dexamphetamine during the critical period of pregnancy and during any other time during pregnancy, and having a child with congenital heart disease. The experimental group consisted of 184 infants which were compared with 108 controls. The serious deficiencies of retrospective studies are recognized by the writers.

179. Nosal, G.
COMPLICATIONS ET DANGERS DES HALLUCINOGÈNES. ASPECTS CYTOPHARMACOLOGIQUES. [Complications and dangers of hallucinogens. Cytopharmacologic aspects.]
Laval Médical, 40: 48-55, 1969.
F - res. pap. - in vivo - sec. disc. - rats - chromosome damage - teratogenicity - exper. admin. - s. c. admin. - extended use - dose/response - stage of devel. - abort. rate - chrom. aberr. - congenit. defects - litter - resorpt. rate - hypothesis B-2816.

The author studies the danger of the hallucinogens (especially LSD) in Sprague-Dawley rats, of causing teratogenic, or any cytogenetic complications. His conclusions are still preliminary, but he was able to note a dose-response relationship in the changes that did occur. It was also found that LSD seemed to have a definite teratogenic effect when administered at the critical period in the development of the fetus. A brief review of the literature on the teratogenic effects of LSD is presented with possible explanations for the discrepancies in the results that exist.

180. Pace, H. B., Davis, W. M., and Borgen, L. A.
TERATOGENESIS AND MARIJUANA.
Annals of the New York Academy of Sciences, 191: 123-131, 1971.
E - gen. pap. - in vivo - tables - rats - chromosome damage - teratogenicity - exper. admin. - s. c. admin. - extended use -

female consumpt. - abort. rate - chrom. aberr. - congenit. defects - litter - placent. funct. - no effect B-2817.

A series of in vivo experiments were done to determine the teratogenic and the chromosome damaging effects of Δ^8- and Δ^9-tetrahydrocannabinols. Groups of rats were subcutaneously injected with doses ranging from 0. 01 to 250 mg. /kg. per day for periods of time ranging from 30 days before conception and continued for 20 days during gestation to administration from just the 10th through the 16th day of gestation. Examination of the offspring and the fetuses of those females sacrificed failed to show any teratogenic effects. Small subdermal hemorrhages on the head and shoulders were observed in the young in a large number of litters but these disappeared within a few days. There was a high mortality rate among the offspring and this was found to be due to the failure of the females to produce sufficient amounts of milk for litter survival. Chromosomes, fertility of the offspring, and the absence of teratogenic consequences on later progeny were all found to be unaffected by the administration of Δ^8- and Δ^9-THC. From the placental transfer studies, it was found that Δ^8- and Δ^9-THC and their metabolites do find their way into the fetus to a limited extent. Finally, marijuana extract was administered subcutaneously on days 6, 7, and 8 of gestation. No abnormalities were found in the fetuses taken prior to birth and in the young observed at birth.

181. Paget, G. E.
DEXAMPHETAMINE SULPHATE IN MICE.
Lancet, 2(7422): 1129, 1965.
E - lett. ed. - in vivo - rabbits - teratogenicity - exper. admin. - congenit. defects - no effect B-2818.

The writer states that an experiment was done in which New Zealand white rabbits were given up to 10 mg. /kg. of dexamphetamine sulphate. No teratogenic effects were found. The contrasting results found when different animal species are used shows that animal studies cannot be relied upon to determine what effects a drug will have on a human fetus. Careful prospective clinical studies with humans are necessary. Drugs should be prescribed with caution and only when necessary for women who may be pregnant.

182. Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C., and Grof, S.
THE EXPERIMENTAL USE OF PSYCHEDELIC (LSD) PSYCHOTHERAPY.
Journal of the American Medical Association, 212(11): 1856-1863, 1970.
E - gen. pap. - in vivo - sec. disc. - tables - humans - chromosome damage - exper. admin. - therapeut. use - single dose - chrom. aberr. - no effect - chrom. analysis, peripheral B-2819.

The work with LSD in psychotherapy is discussed under the headings: "Effects in Man Facilitated by Psychedelic Drugs", "The Varieties of Psychedelic Drug Therapies", "Research Projects With Psychedelic-Peak Psychotherapy", "Report of a Case", and "The Question of Safety". White blood cell chromosomes were analysed in 32 patients before and after the administration of pure LSD as treatment and in 5 chronic LSD users who acted as research subjects. In addition, chromosome analysis was performed on eight normal experimental subjects who were given pure LSD. No increase over the normal chromosomal breakage rate was found. The mean chromosomal aberration rate before and after administration only varied from 2.65 to 5.91 percent.

183. Papirmeister, B., and Wolpert, J. S.
LYSERGIC ACID DIETHYLAMIDE: PHOTODYNAMIC INACTIVATION OF REPAIR DEFICIENT E. COLI AND T1 BACTERIOPHAGE.
Biochemical and Biophysical Research Communications, 38(2): 319-327, 1970.
E - res. pap. - in vivo - chromosome damage - exper. admin. - dose/response - chrom. aberr. - no effect - hypothesis B-2820.

Bacterial strains were used in this experiment to determine if LSD sensitization has any effect on the repair mechanisms of chromosomes damaged by irradiation. The derivatives of E. coli B and T1 bacteriophage are listed and the techniques for growing the bacteria, for adding the LSD, and for the preparation of the plates for irradiation are given. The differences in the sensitivities of these derivatives to ultraviolet light are due to mutations at the 3 loci in the bacterial chromosome. The hypothesis was that if the photodynamic action of the ultraviolet light on the LSD-sensitized organisms were also to produce DNS damage subject to dark repair, different responses from the various bacterial derivatives might be expected. This hypothesis was confirmed. The implication of these results is that DNS was the target in the photodynamic inactivation of LSD-sensitized bacteria. This high susceptibility of bacter-

ia to this photodynamic damage suggests an intimate association of LSD with genetic material. It was noted, however, that the high dose of LSD used failed, on its own, to produce detectable DNA damage.

184. Perlmutter, J. F.
DRUG ADDICTION IN PREGNANT WOMEN.
American Journal of Obstetrics and Gynecology, 99(4): 569-572, 1967.
E - gen. pap. - gen. disc. - humans - female - male - teratogenicity - intent. use - female consumpt. - congenit. defects - death - fetocidal - premature birth - no effect - birth, pre term. - birth, full term B-2821.

Twenty-two heroin-addicted women admitted to the obstetrical service of a hospital over a period of two years were studied. Their ages ranged from 21 to 38 years and their average length of addiction was 3 years, 10 months. It was found that their previous pregnancy wastage rate was 24 percent. This wastage could not, however, be correlated with known addiction in the women. In the group studied, 56.5 percent of the infants weighed less than 2,500 gms. The average weight was 2,296 gms. The perinatal mortality rate was 17.4 percent with one stillbirth and three neonatal deaths. Of the babies that survived, 54.5 percent showed signs of withdrawal. Three infants had congenital anomalies. One child had a positive phynylketonuria, animperforate anus, a rectovaginal fistula, and cataracts, the second had an inguinal hernia, and the third had paraphimosis.

185. Persaud, T. V. N., and Ellington, A. C.
CANNABIS IN EARLY PREGNANCY.
Lancet, 2(7529): 1306, 1967.
E - lett. ed. - in vivo - mice - teratogenicity - exper. admin. - i.p. admin. - single dose - fetal maldevel. - resorpt. rate - no effect - birth, pre term. B-2822.

The writer gives the results of administering cannabis resin intraperitoneally to pregnant mice on day 6, or from day 1 to day 6 of gestation. With the single 16 mg./kg. dose, there was a high incidence of overall stunting. No apparent malformations in the fetuses and no reduction in litter size were observed. When the dose was given daily, complete fetal resorptions in the animals were observed.

186. Persaud, T. V. N. , and Ellington, A. C.
THE EFFECTS OF CANNABIS SATIVA L. (GANJA) ON DEVELOPING RAT EMBRYOS - PRELIMINARY OBSERVATIONS.
West Indian Medical Journal, 17: 232-234, 1968.
E - res. pap. - in vivo - rats - teratogenicity - exper. admin. - i. p. admin. - extended use - female consumpt. - congenit. defects - fetal maldevel. - resorpt. rate - birth, pre term. B-2823.

An experiment was done in which pregnant albino rats were intraperitoneally administered 4. 2 mg. /kg. of cannabis resin daily from days 1 to 6 of gestation. The females were sacrificed on the 12th day of gestation and the number of corpora lutea, fetal resorptions, and fetuses recovered were recorded. A high incidence of overall stunting, syndactyly, encephalocoele, phocomelia, and hernia of the anterior abdominal wall were observed. Fetal resorption accounted for 29 percent of all implantations.

187. Persaud, T. V. N. , and Ellington, A. C.
TERATOGENIC ACTIVITY OF CANNABIS RESIN.
Lancet, 2(7564): 406-407, 1968.
E - lett. ed. - in vivo - rats - teratogenicity - exper. admin. - i. p. admin. - extended use - female consumpt. - congenit. defects - fetal maldevel. - resorpt. rate - birth, pre term. B-2824.

In a letter, the writer tells of an experiment in which pregnant albino rats were intraperitoneally administered 4. 2 mg. /kg. of cannabis resin daily from day 1 to day 6 of gestation. The females were sacrificed on the 12th day of gestation and the fetuses examined. Incidence of fetal malformations, resorption of fetuses, and retarded development in the treated animals were significantly higher than in the controls. It was found that the incidence of congenital abnormalities was: stunting, 100 percent; syndactyly, 72 percent; encephalocele, 57 percent; eventation of abdominal viscera, 30 percent; phocomelia, 15 percent; and amelia, 2 percent. Cannabis resin is teratogenic.

188. Poland, B. J. , Wogan, L. , and Calvin, J.
TEENAGERS, ILLICIT DRUGS AND PREGNANCY.
Canadian Medical Association Journal, 107: 955-958, 1972.
E - res. pap. - in vivo - humans - female - male - teratogenicity - intent. use - extended use - female consumpt. - death - fetal maldevel. - premature birth - birth, pre term. B-2825.

A prospective study was carried out with 99 pregnant subjects who had: 1) discontinued drug use before pregnancy, 2) used drugs up

to and during the first 20 weeks of pregnancy, and 3) used drugs throughout pregnancy. A full social history and a history of drug use were obtained. The drugs that were abused were hallucinogens, sedatives, tranquillizers, stimulants, and narcotics. These subjects were compared with 84 controls who were between the ages of 14 and 23 years. The infants born to the drug users showed a significant preponderance of females. Thirteen percent were born prematurely and 3 out of this group died. There was one stillbirth. There was no significant increase in the frequency of congenital anomalies nor was there a specific anomaly predominant.

189. Prince, A. M.
LSD AND CHROMOSOMES.
Psychedelic Review, 9: 38-40, 1967.
E - gen. pap. - gen. disc. - humans - chromosome damage - exper. admin. - intent. use - single dose - chrom. aberr. - no effect - chrom. analysis B-2826.

The author comments on the experiment done by M. M. Cohen et al. and reported in the March 17, 1967 issue of Science along with the further publicizing of the results in other magazines. It is first pointed out that firm conclusions cannot be made until the findings are repeated by other laboratories. This had not yet been done. The objectivity of the experimenters is questioned along with the significance of using such high doses of LSD over such long exposure periods. The large increase in frequency of chromosomal breakage in the treated cultures was significant. However, the lack of a consistent effect on frequency of breaks is disturbing. Only one control figure was used throughout the experiment and no explanation of how it was arrived at was given. This point was commented upon as well as the significance of chromosome breakage, in general. The data given does constitute a warning but more work must be done.

190. Quinn, N. C.
LSD: CHROMOSOMAL BREAKS IN ANTHERAEA EUCALYPTI (SCOTT). (LEPIDOPTERA: SATURNIIDAE).
Entomological News, 81: 241-242, 1970.
E - res. pap. - in vitro - tables - chromosome damage - exper. admin. - single does - chrom. aberr. - chrom. aberr. - chrom. analysis B-2827.

Cultures of Antheraea eucalypti cells from the ovaries of diapausing pupae were treated with an aqueous solution of LSD for five hours. After a five hour recovery period, the cultures were prepared for

examination to determine if there were any structural defects. Control cultures underwent indentical test conditions with the exception of the LSD. Structural aberrations, the majority of which were chromosome breaks, were observed within many of the cells. Most breaks occurred near the primary constriction. Scattered incidents of mitotic ruffling were also detected.

191. Rappaport, B. S.
LSD AND CHROMOSOMES.
New England Journal of Medicine, 278(4): 222-223, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - exper. admin. - chrom. aberr. - no effect - chrom. analysis B-2828.

A medical student questions the validity of the conclusions of Cohen et al. that chromosomal damage is induced by LSD in vitro and in vivo. He notes a lack of correlation between dose, exposure time, and effect and also the inaccuracy in relating in vitro concentrations, over a wide range, to in vivo concentrations. He also notes the unexplained similarity in the percentage of breaks of users of LSD and in other drug users. He feels that the fact that chromosome damage was incurred regardless of which drugs were taken with LSD argues against the incrimination of LSD, as this is like concluding that "water is inebriating because it has the same effect whether consumed with scotch or rye".

192. Riley, H. P., and Neuroth, J. V.
LSD AND PLANT CHROMOSOMES.
Journal of Heredity, 61(6): 283-284, 1970.
E - reg. pap. - in vivo - tables - plants - chromosome damage - exper. admin. - single dose - chrom. aberr. - no effect - chrom. analysis B-2829.

Experiments were done on the effects of LSD on the chromosomes of Vicia faba and Allium cepa. The Vicia faba seeds were allowed to germinate in vermiculite and the Allium cepa root tips were grown in tap water. LSD was added in various concentrations from 0.01 to 50 mg./l. for exposure periods of from one to eight hours. The Vicia faba roots were allowed to recover for one hour and the Allium cepa roots were allowed three days to recover. A table is provided showing the number of chromosome aberrations per total number of cells studied with the different treatments of LSD. With certain treatments, only a small number of metaphases could be analysed. However, the number that could be scored showed no correlation with the treatments but seemed to be determined more by the state of the individual root and the technique. Only one small

deletion was found in all the treatments. LSD did not cause chromosome aberrations in these plant roots.

193. Robson, J. M.
TESTING DRUGS FOR TERATOGENICITY AND THEIR EFFECTS ON FERTILITY. THE PRESENT POSITION.
British Medical Bulletin, 26(3): 212-216, 1970.
E - gen. pap. - sec. disc. - hamsters - humans - mice - chromosome damage - teratogenicity - exper. admin. - intent. use - female consumpt. - chrom. aberr. - congenit. defects - no effect
B-1332.

Regulations of the FDA (U. S. A.) are outlined and procedures are evaluated in comparison with the British regulations dealing with the predictive value of toxicity tests of new drugs and pesticides. The U. K. will accept teratological studies alone while the U. S. A. requires fertility, teratological, peri- and post-natal studies. The U. K. suggests at least 3, the U. S. A. only 2, dose levels. Tests on more than one species is usual. Interpretation of the results is discussed. Criteria, such as an LD_{50}/teratogenic dose ratio, are suggested. Reports on teratogenic effects of LSD and mescaline are cited. The LD_{50} of LSD is of the order of 54 mg. /kg. while the teratogenic dose is very small at around 0. 1 μg. /kg. This gives a very high teratogenic ratio of over 500, 000 and the drug should be rejected. It is suggested that studies on metabolism and elimination of drugs be added to those on teratogenesis as an aid to relating results of animal experiments to man. Mechanisms by which drugs produce embryotoxic and teratogenic effects are mentioned.

194. Roloff, D. W., and Howatt, W. F.
THE EFFECT OF CHRONIC MATERNAL MORPHINE ADMINISTRATION ON LUNG DEVELOPMENT AND GROWTH OF FETAL RABBITS.
Pediatric Research, 7(4): 321, 1973.
E - abst. - in vivo - rabbits - teratogenicity - exper. admin. - s. c. admin. - extended use - female consumpt. - fetal maldevel. - no effect - birth, pre term. B-2830.

An abstract is given of an in vivo experiment with rabbits in which 2. 5 to 10 mg. /kg. of morphine was subcutaneously injected every 6 hours from the end of the first week to the 27th, 28th, or 29th day of gestation. The maximum volume of air entering the fetal lungs (V_{max}) and the proportion of air remaining after a deflation pressure of 10 cm. of H_2O (V_{10}/V_{max}) were used to reflect fetal lung maturity. The weights of all the fetuses were also recorded. At

28 days of gestation, V_{max} and V_{10}/V_{max} values were lower for fetuses of morphine treated females than in the controls. Maternal morphine addiction in rabbits interferes with fetal lung maturation as well as fetal growth.

195. Rossi, G. V.
LSD - A PHARMACOLOGIC PROFILE.
American Journal of Pharmacy, 143(2): 38-44, 1971.
E - gen. pap. - sec. disc. - humans - chromosome damage - teratogenicity - exper. admin. - intent. use - therapeut. use - abort. rate - chrom. aberr. - congenit. defects - no effect - chrom. analysis, peripheral - chrom. analysis, bone mar. B-2831.

The pharmacologic aspects of LSD are discussed under the headings: "General Pharmacology in Man", "Psychopharmacologic Effects", and "Adverse Reactions". It is stated that the relationship between LSD, chromosomal damage, leukemogenicity, and teratogenicity remain unresolved. However, a positive relationship has been found between the use of illicit LSD and chromosomal aberrations. With illicit LSD, the dose cannot be ascertained and the samples may contain impurities or contaminants. In addition, these subjects are frequently multiple drug users. Pure LSD administered in clinical settings has failed to produce lymphocyte chromosome damage. It was noted that transient chromosomal breaks in leukocytes occur spontaneously and that the pathological significance of damage in continuously replenished leukocytes is equivocal. The effects of LSD on human pregnancy and birth defects remains controversial. Several teratogenic studies are discussed.

196. Roux, C., Dupuis, R., and Aubry, M.
LSD: NO TERATOGENIC ACTION IN RATS, MICE, AND HAMSTERS.
Science, 169(3945): 588-589, 1970.
E - gen. pap. - in vivo - tables - hamsters - mice - rats - teratogenicity - exper. admin. - s. c. admin. - extended use - abort. rate - congenit. defects - fetal maldevel. - no effect - birth, pre term. B-2832.

Reports are cited on the teratogenic action of LSD in animals, on criticism of the methods of investigation, and on negative results reported by some researchers. The two reported cases of limb deformity in babies of users are noted along with the positive and negative effects on chromosomes by LSD. A causal relationship is not established. LSD tartrate was injected subcutaneously into 98 pregnant rats, 67 mice, and 22 hamsters in a single dose of 5

to 500 μg./kg. per day either at the beginning of gestation or during the period of ganogenesis (the time depending on the species). Examination of the 1003 rat fetuses revealed a few malformed offspring but not a statistically significant number, and of 521 mouse fetuses and 189 hamster fetuses failed to prove any abortifacient, teratogenic, or growth-depressing effects. This does not preclude a teratogenic in man.

197. Ruffié, J., Colombies, P., and Grozdea, J.
ACTION EXPÉRIMENTALE DU DIÉTHYLAMIDE DE L'ACIDE LYSERGIQUE (LSD 25) SUR LES LEUCOCYTES DU SINGE PAPIO PAPIO. [Experimental action of lysergic acid diethylamide (LSD 25) on the leukocytes of the Papio papio baboon.]
Bulletin de l'Académie Nationale de Médecine, 155(9-10): 180-189, 1971.
F - res. pap. - in vivo - review - tables - primates - chromosome damage - exper. admin. - s. c. admin. - single dose - congenit. defects - chrom. analysis, peripheral B-2833.

Although numerous studies have been done on the effect of LSD on chromosomes, there still does not exist unanimous agreement in the results. The authors of this study performed experiments on the leucocytes of the circulating blood of the Papio papio baboon. LSD was subcutaneously injected in one female adult and three male adults and results were compared with seven control animals. Four to eight weeks after the injection, results from cytochemical analysis, from reactivity of the lymphocytes to phytohemagglutinine, and from chromosome anomalies examinations were given. There were definite metabolic anomalies, occasionally accompanied by profound modifications noted. It must be noted that it is not possible to know if the anomalies always disappear after the elimination of the drug, a fact which could have more serious implications.

198. Sato, H., and Pergament, E.
IS LYSERGIDE A TERATOGEN?
Lancet, 1(7543): 639-640, 1968.
E - lett. ed. - case rep. - tables - humans - female - chromosome damage - intent. use - oral admin. - extended use - female consumpt. - chrom. aberr. - birth, full term B-2834.

To add to the few case reports previously given and cited in this letter, of offspring born to mothers who had taken LSD before or during pregnancy, the author presents a new case. A 20 year old mother took psychedelic doses of LSD 5 times during pregnancy and before. She had also taken 60 contraceptive pills. A full term

healthy girl was born. Karyotypic analysis of the mother and baby was started on the 2nd day after birth. Compared to control samples, there was no increase in gaps, breaks, or other structural aberrations. However, aneuploidy (loss of chromosomes from the complement) was significantly greater. There was no history of viral infection or irradiation. More data on the effects of LSD in pregnancy is required.

199. Sato, H., Pergament, E., and Nair, V.
LYSERGIC ACID DIETHYLAMIDE IN PREGNANCY.
Federation Proceedings; Federation of American Societies For Experimental Biology, 28(2): 549, 1969.
E - abst. - in vivo - rats - chromosome damage - teratogenicity - exper. admin. - oral admin. - s.c. admin. - single dose - extended use - female consumpt. - chrom. aberr. - congenit. defects - litter - no effect - chrom. analysis - chrom. analysis, bone mar. B-2835.

An abstract is given of an experiment in which LSD was orally or subcutaneously administered to female rats in doses of 100 μg./kg. on the 4th and 5th days of gestation, or the 4th or the 8th day. The females in the double dosage group were sacrificed on the 14th or 15th day and the females in the second group were allowed to deliver their offspring. Chromosome analysis was performed on the embryonic tissues of the offspring of the first group and on the bone marrow cells of the females in both groups along with the 8 to 15 week old offspring of the second group of females. Examination of 1174 embryonic cells and 1498 bone marrow cells failed to show a significant alteration in the distribution of chromosome number or to show a significant increase in structural chromosome aberrations. In addition, there was not a significant increase of congenital abnormalities in the embryos of the LSD treated rats.

200. Sato, H., Pergament, E., and Nair, V.
LSD IN PREGNANCY: CHROMOSOMAL EFFECTS.
Life Sciences, Part II: Biochemistry, General and Molecular Biology, 10(13): 773-779, 1971.
E - res. pap. - in vivo - tables - rats - chromosome damage - exper. admin. - oral admin. - single dose - female consumpt. - chrom. aberr. - no effect - birth, pre term. - birth, full term - chrom. analysis, bone mar. B-2836.

An experiment was done with female rats and their offspring. LSD was orally administered in a single dose of 100 μg./kg. on the 4th or 8th day of gestation and one group of females was sacrificed on

the 14th or 15th day of gestation with the second group allowed to give full term births. Femur bone marrow cells were obtained from the sacrificed females, from the embryos of the sacrificed females, and from the 8 to 15 week old offspring of the surviving females. In all areas of investigation, control animals were paired with LSD treated animals. Slides of the cells were analysed without knowledge of their source. There was no statistically significant difference in the distribution of the chromosome numbers in the cells of the LSD treated rats. In addition, there was no increase in structural chromosomal aberrations in the cells of the pregnant females and their offspring. A table of the results is provided. The authors reported that they had the opportunity of examining the peripheral leukocytes of a male and pregnant female LSD users. Chromosomal analysis revealed no abnormalities and the child was born with no congenital malformations. Other studies are cited which also presented negative results but it was felt that the positive findings found by others could not be ignored.

201. Shapiro, L. R., and Kerr, J.
LSD AS A POSSIBLE MUTAGEN INSTEAD OF A TERATOGEN.
Pediatric Research, 6(4): 363, 1972.
E - abst. - gen. disc. - humans - teratogenicity - intent. use - male consumpt. - congenit. defects - birth, full term B-2837.

An abstract is provided in which the writer presents support for two previous cases in which children, born to parents who had used LSD during pregnancy, were found to have congenital defects. The writer reports on two infants who suffered tibial aplasia and fibular aplasia or hypoplasia. The mothers denied the use of LSD or other drugs but the fathers were found to have used LSD before the conception of the children. Chromosome analyses of both infants were normal. From this evidence, it is suggested that if LSD was responsible, the drug may act as a mutagen rather than a teratogen.

202. Singh, M. P., Kalia, C. S., and Jain, H. K.
CHROMOSOMAL ABERRATIONS INDUCED IN BARLEY BY LSD.
Science, 169(3944): 491-492, 1970.
E - gen. pap. - in vivo - tables - plants - chromosome damage - exper. admin. - single dose - chrom. aberr. - chrom. analysis B-2838.

Conflicting reports of the genetic effects of LSD and one reviewing most of the literature dealing with this area, are cited. Seeds of barley were germinated overnight, then treated with an aqueous solution containing 25 μg./ml. of LSD for either 4 or 8 hours.

After a corresponding 4 or 8 hour recovery period, preparations of squashed root tips were stained with Feulgen. There were extensive chromosomal aberrations, most of which were chromosome breaks, which were not randomly located on the chromosomes. Nearly half occurred in the region of the primary constriction, resulting in many apparently acentric fragments. These results conflict with the negative effects of LSD on chromosomes in the broad bean cells, the only other plant study reported.

203. Siva Sankar, D. V., Rozsa, P. W., and Geisler, A.
CHROMOSOME BREAKAGE IN CHILDREN TREATED WITH LSD-25 AND UML-491.
Comprehensive Psychiatry, 10(5): 406-410, 1969.
E - res. pap. - in vivo - tables - humans - chromosome damage - therapeut. use - extended use - chrom. aberr. - no effect - chrom. analysis, peripheral B-2839.

Conflicting reports on the effects of LSD on chromosomes are cited. A new study of leukocyte mitotic chromosomes in psychiatric patients in a children's unit is presented. Fifteen patients (ages 7 to 15 years) received 37.5 to 165.8 μg./day of LSD for 2 to 1366 days, 9 patients received UML-491, and 8 patients received both. Chromosome studies were done 2 to 4 years after treatment had stopped. There were 25 psychiatric patients on no medication, 7 adult employees, and one normal 14 year old, who were used as the controls. In the LSD group, there was 0.8 percent breaks, in the UML-491 group, 0.56 percent breaks, and 1 percent in those on both drugs. There were 0.68 percent breaks in the non-medicated children and 0.57 percent in the adults. The differences were not statistically significant. Factors accounting for different reports are discussed. They may involve laboratory techniques, purity of LSD, multiple drug use, and the time between the last ingestion and the sampling which might provide enough time for the repair of any damage.

204. Skakkebaek, N. E., and Philip, J.
LSD IN MICE: ABNORMALITIES IN MEIOTIC CHROMOSOMES.
Science, 160(3833): 1246-1248, 1968.
E - gen. pap. - in vivo - tables - mice - chromosome damage - exper. admin. - injection - single dose - extended use - male consumpt. - chrom. aberr. - spermatogen. effect - chrom. analysis B-2840.

Reports were cited on the effects of LSD on chromosomes in leukocytes, congenital defects in animals, and the possible effects

on human embryos. Six male mice 6 to 8 weeks old were injected with 1 mg./kg. of LSD. The number of injections varied. Preparations of meiotic chromosomes were made. Several breaks, gaps, and unidentifiable fragments were found in the treated but not in the six control mice, with a few exceptions. Secondary constrictions were more numerous in the treated than in the untreated mice. These preliminary results using a high dose with few animals suggest that LSD can cause changes in the meiotic chromosomes in germ cells. The chromosomal abnormalities were mainly found in diakinesis or metaphase I, and most were on the X chromosome. The findings in studies of meiotic chromosomes by other researchers, after treatment with streptonigrin, cyclophosphamid, and triziquon resemble those in this first known study of LSD and meiotic cells.

205. Skakkebaek, N. E., and Beatty, R. A.
STUDIES ON MEIOTIC CHROMOSOMES AND SPERMATOZOAN HEADS IN MICE TREATED WITH LSD.
Journal of Reproduction and Fertility, 22: 141-144, 1970.
E - gen. pap. - in vivo - tables - mice - chromosome damage - exper. admin. - s. c. admin. - extended use - male consumpt. - chrom. aberr. - spermatogen. effect - chrom. analysis B-2841.

An experiment is reported in which four 6 to 8 week old male mice were subcutaneously injected with 1 mg./kg. of LSD twice a week for five weeks. Two days after the last injection the mice were hemicastrated and meiotic preparations were made for the eight tests. Both chromosomal and spermatozoan morphology were studied. Two hundred cells in diakinesis or metaphase I and 100 cells in metaphase II were scored in each mouse except one. There was a high frequency of abnormalities in two of the LSD treated mice. Large variations in effects have also been shown in other studies. The slides of the cells of the LSD treated mice, in the spermatozoa study, could be distinguished in 7 out of the 8 cases because the spermatozoa had a more rounded convex side of the head and had broader heads in comparison with the controls. It is not known whether these results were due to the effects of LSD on spermiogenesis, on the testis, or on the whole body.

206. Slatis, H. M.
CHROMOSOME DAMAGE BY LSD.
Science, 159: 1492-1493, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - intent. use - chrom. aberr. - no effect - chrom. analysis, peripheral B-2842.

Loughman's results, which led him to conclude that there was no correlation between the use of LSD and chromosome damage in vivo, were re-examined. His method of statistical analysis and his use of only one control are criticized. The facts, re-interpreted, actually support the positive findings of others.

207. Smart, R. G., and Bateman, K.
THE CHROMOSOMAL AND TERATOGENIC EFFECTS OF LYSERGIC ACID DIETHYLAMIDE: A REVIEW OF THE CURRENT LITERATURE.
Canadian Medical Association Journal, 99: 805-810, 1968.
E - gen. pap. - review - hamsters - humans - mice - rats - chromosome damage - teratogenicity - exper. admin. - intent. use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - no effect - chrom. analysis B-2843.

Six of 8 studies (7 using human leukocytes) reported that LSD, when added in vitro, damaged chromosomes. Some studies of chromosomes of users also indicated a high incidence of abnormalities. In one, with 50 users and 14 controls, the mean breakage rate for the users was twice that for the controls. However, two groups of researchers found no effect. The positive and negative results are difficult to reconcile. Questions of dose and counting methods are discussed in relation to discrepancies. The effect of chlorpromazine and other drugs is mentioned. An offspring of a father and mother who took LSD was born with a deformed leg. Both parents and child had chromosome breaks. Studies in rats, mice, and hamsters are assessed. Three found that LSD had a teratogenic effect when given early in pregnancy and one did not. More studies are urged correlating chromosomal and teratogenic effects, and using germ cells as well as leukocytes. The evidence for a teratogenic effect of LSD is strong but not conclusive.

208. Smit, E. M., and Borst, P.
LSD-25 DOES NOT INTERCALATE IN DNA.
Nature, 232(5307): 191-192, 1971.
E - gen. pap. - in vitro - chromosome damage - exper. admin. - chrom. aberr. - no effect - chrom. analysis B-2844.

An experiment was undertaken to determine if LSD intercalated in DNA. LSD was added to twisted, circular, covalently closed duplex DNA in a viscometer. The effect of LSD was compared to that of the intercalating dye ethidium on the closed circular duplex of bacteriophage PM2. No interaction between DNA and LSD was detectable with concentrations with which strong interaction was

found using other intercalating chemicals. When the interaction between LSD and DNA was studied spectrophotometrically, the spectra was the exact summation of the two separate components. It was concluded that chromosome damage with LSD was not a consequence of the intercalation of LSD into DNA. Due to the observation that irradiation of DNA with ultraviolet light in the presence of LSD led to phosphodiester bond breakage, it was suggested that LSD dependent photo destruction of DNA could contribute to chromosome damage in cells exposed to in vitro or in vivo studies.

209. Sparkes, R. S., Thomas, D., Melnyk, J., and Bozzetti, L.
CHROMOSOMAL EFFECT AND LSD: SAMPLES OF FOUR.
Science, 162: 1509, 1968.
E - gen. pap. - gen. disc. - humans - chromosome damage - intent. use - chrom. aberr. - no effect - chrom. analysis B-2845.

The writers respond to criticism of their statistical methods used in their previous experiment. They give additional support for their previous statistical techniques which were based on the null hypothesis that LSD should have no damaging effect on chromosomes, the standard five percent confidence limit, a skewed distribution, and on their inability to obtain a completely random selection. Further clarification of the procedures used in the experiment is made. There is no reason to change the conclusion that the studies undertaken have not shown that LSD causes chromosomal damage.

210. Sparkes, R. S., Melnyk, J., and Bozzetti, L. P.
CHROMOSOMAL EFFECT IN VIVO OF EXPOSURE TO LYSERGIC ACID DIETHYLAMIDE.
Science, 160(3834): 1343-1345, 1968.
E - gen. pap. - in vivo - humans - chromosome damage - intent. use - therapeut. use - extended use - female consumpt. - male consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2846.

Conflicting reports on the effects of LSD on chromosomes in vivo and in vitro are cited. Negative results are reported in a study comparing chromosomes in the blood of four illicit users, four psychiatric patients treated with LSD and four controls. Most of the users had also taken other drugs. Different techniques and counting methods are outlined. There was no significant difference between the two groups of LSD users and the control group with respect to the number of aberrations that were found. However, quadriradials were seen only in the LSD users. Results from other laboratories may be due to different media, different susceptibility

of the users, or environmental factors. The relevance of in vitro experiments with lymphocytes in regards to genetic effects is questioned. Studies on meiotic cells and on children of users are suggested to better establish whether there is an effect on the gametes.

211. Spindler, J. S., and Garcia Monge, M. T.
EFFECTS OF DOM (STP) ON THE CHICK EMBRYO.
Bulletin on Narcotics, 22(1): 55-60, 1970.
E - res. pap. - in vivo - mammals - teratogenicity - exper. admin. - single dose - congenit. defects - embryocidal - embryo. maldevel. - birth, pre term. - birth, full term B-2847.

An experiment was done to determine the teratogenic effects of DOM (STP) on the developing chick embryo. The embryos were at the 5th stage of development and were administered with either 0.05 or 0.5 mcg./1/4 cc. of DOM. There were four groups having 26 embryos in each for each dosage. An equal number of controls were set up and given 1/4 cc. of buffered sterile tyrode solution. At intervals of 24, 48, 72, and 114 hours, a group from each dosage level was examined. A description of certain fundamental features of normal development during stages 5, 13, 18, and 28 is given. Figures of deformed embryos are presented. Descriptions of deformed embryos with specific types of anomalies are given. The percentage of dead embryos was 45.19 percent of the 208 embryos found. Mortality was higher during the long incubation period. Of the 114 living embryos, 93 showed some degree of abnormality. Of the total number of embryos, the incidences of the various types of anomalies were: anencephalia, (roughly) 21.6 percent; microphthalmia, 17.3 percent; spina bifida, 11.52 percent; microsomia, 8.17 percent; and rachischisis, 0.48 percent. In some cases there was atrophy of the embryo. There was also a high percentage of localized haemorrhages found mainly in the cephalic, cervical, thoracic, and abdominal regions. DOM was teratogenic in chicken embryos.

212. Srám, R. J.
MUTAGENIC EFFECT OF LSD IN DROSOPHILA MELANOGASTER.
Activitas Nervosa Superior, 12(3): 265-266, 1970.
E - gen. pap. - in vivo - fruit flies - chromosome damage - exper. admin. - injection - single dose - male consumpt. - chrom. aberr. - chrom. analysis B-2848.

Day old male Drosophila were injected on the dorsal side of the

abdomen with 0.2 μl. volume of LSD and were immediately mated to virgin females and transferred to fresh virgins until seven broods were obtained. The results of the sex-linked recessive lethal test were negative at both applied concentrations of 50 or 500 μg./ml. In the eucentric aberrations test at 500 μg./ml., there was found in the brood corresponding to meiosis, a six fold increase in the frequency of nondisjunction, and a twenty fold increase in losses of X and Y chromosomes. The deletions of Y chromosomes were in the range of the spontaneous mutation rate. The conclusion, that LSD at very high concentrations is a weak mutagen for genes and chromosomes, agrees with other reports cited.

213. Srám, R. J., and Zudová, Z.
INDUCTION OF DOMINANT LETHALS AND TRANSLOCATIONS IN MICE.
Activitas Nervosa Superior, 13(3): 212-213, 1971.
E - gen. pap. - in vivo - tables - mice - chromosome damage - exper. admin. - i.p. admin. - single dose - male consumpt. - chrom. aberr. - spermatogen. effect - birth, pre term. B-2849.

An experiment was done in which the dominant lethal test and a cytological analysis of changes induced in spermatogonia were used to determine the genetic effects of LSD. Three groups of mice, with 25 males in each, were intraperitoneally administered 0.01, 0.1, and 1.0 mg./kg. of LSD. Each male was then mated with two different females each week for eight weeks. The females were sacrificed on the 14th day of gestation. The numbers of corpora lutea in the ovaries, viable, and resorbed embryos in the uterus were recorded. Ten males which were given 1 mg./kg. of LSD were killed 12 weeks after treatment and meiotic preparations were made. The dose of 1 mg./kg. of LSD induced a significant increase in total dominant lethality at the stage of early spermatids, especially due to the increase of preimplantation dominant lethality. Translocations were not found in spermatocytes nor were breaks or gaps found in the X chromosome. LSD induced no chromosomal rearrangements at the stage of spermatogonia and only moderately increased the frequency of dominant lethals at the postmeiotic stage of spermatogonia.

214. Srám, R. J.
LSD: INDUCTION OF MOSAIC MUTATIONS IN THE SPERMATOZOA OF DROSOPHILA MELANOGASTER.
Activitas Nervosa Superior, 13(3): 213-214, 1971.
E - gen. pap. - in vivo - tables - fruit flies - chromosome damage

- exper. admin. - injection - single dose - male consumpt. - chrom. aberr. - spermatogen. effect B-2850.

An experiment was done in which male fruit flies were injected with .2 μl. of LSD. Some of them were mated immediately with Muller-5 virgin females and these were submitted to the ordinary Muller-5 test. The rest of the males were mated in mass. Mosaics were determined by mating nonlethal Muller-5 cultures of F2 generation to several pair cultures to obtain F3 generations. Full lethals and mosaics were remated for confirmation of the effects. Dumpy locus determinations were also made. There was a significant mutation frequency of full and mosaic sex-linked recessive lethals and mutations in the dumpy locus at the second chromosome. These effects correspond to an almost two-fold mutagenic activity of LSD. Tables are provided.

215. Stenchever, M. A., and Jarvis, J. A.
LYSERGIC ACID DIETHYLAMIDE (LSD). EFFECT ON HUMAN CHROMOSOMES IN VIVO.
American Journal of Obstetrics and Gynecology, 106(4): 485-488, 1970.
E - res. pap. - in vivo - tables - humans - chromosome damage - intent. use - extended use - female consumpt. - male consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2851.

Chromosome analysis was performed on 12 LSD users and a 1 1/2 year old child who was exposed to LSD in utero. Their ages ranged from 18 to 31 years while the ages of the control group ranged from 17 to 45 years. The number of exposures ranged from 2 to 70 and the average dose ranged from 350 to 1000 μg. The shortest time since the last exposure was one week and the longest time was 22 months. Other drugs had been used in four cases. The preparation of the blood leukocytes cultures is described and tables of the clinical data and the results are provided. No significant differences were found in the gap or break rates between the experimental and control groups. In addition, no abnormal forms were seen in the experimental group. The complications inherent in in vivo studies are discussed. The difficulty of comparing in vivo and in vitro data is also mentioned.

216. Stenchever, M. A., and Allen, M.
THE EFFECT OF DELTA-9-TETRAHYDROCANNABINOL ON THE CHROMOSOMES OF HUMAN LYMPHOCYTES IN VITRO.
American Journal of Obstetrics and Gynecology, 114(6): 819-821, 1972.

E - res. pap. - in vitro - tables - humans - chromosome damage - exper. admin. - single dose - chrom. aberr. - no effect - chrom. analysis, peripheral B-2852.

An experiment was done to determine the effect of delta-9-tetrahydrocannabinol (Δ^9-THC) on human leukocyte cells. Enough blood for five cultures was obtained from each of the four normal subjects ranging in age from 19 to 33 years. Δ^9-THC in ethanol was added in concentrations of .1, 1.0, 10.0, 100.0 μg./ml. and the last culture of each of the four sets was given a final concentration of 0.1 percent ethanol as a control. Slides were prepared, coded for blind scoring, and scored for breaks, gaps, and the presence of abnormal forms. A table of the results is provided. No growth in the four 100 μg./ml. concentration cultures was seen. The remaining cultures showed a good mitotic index and no significant increase in chromatid or isochromatid breaks or gaps was found. No abnormal forms were observed. No evidence of chromosome damage could be found with pure Δ^9-THC in vitro.

217. Stubbs, V., and Jacobson, C. B.
LSD AND GENETIC DAMAGE.
Perspectives on Drugs and Drug Use, 3: 23-29, 1970.
E - gen. pap. - gen. disc. - tables - humans - chromosome damage - teratogenicity - intent. use - female consumpt. - male consumpt. - chrom. aberr. - embryo. maldevel. - carcinogen. effect - no effect B-2853.

This paper concerns the effects of LSD on genetic damage. The retrospective study which was being done by the second author was mentioned. Seventy LSD using pregnant women and a smaller number of fathers were under examination. The familial, social, and psychological similarities and differences with the control group are discussed. The difficulty in obtaining reliable information concerning drug usage is outlined. Terminology corresponding to the genetic risk resulting from LSD ingestion is defined and discussed. The terms include: mutagenesis, somatoxic, carcinogenic, teratogenic, and reproductive detriment. A repetitive central nervous system defect has been found in 4 of 15 intact embryos of LSD users. This major abnormality could explain the increased incidence of early spontaneous abortion in LSD users. Possible genetic changes in the embryo gonadal tissues may not be demonstrated for several generations. It has been shown that any chromosome breaking agent will shorten cellular life if chronically applied. Thus, a high incidence of leukemia could be expected in chronic LSD users. The problems involved with illicit drug use and the responsibilities of communities and individuals are discussed.

218. Sturelid, S., and Kihlman, B. A.
LYSERGIC ACID DIETHYLAMIDE AND CHROMOSOME BREAKAGE.
Hereditas, 62(1-2): 259-262, 1969.
E - gen. pap. - in vivo - in vitro - tables - hemastes - humans - plants - chromosome damage - exper. admin. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2854.

Experiments on the effects of LSD on chromosomes were done with lateral roots from the broad bean, with male hamster embryonic lung cells, and with human peripheral blood cultures. The roots were exposed to 1, 10, and 50 mg./l. of LSD for varying durations of time, the hamster cells were exposed to 10 and 20 mg./l. of LSD for 2, 24, and 48 hours, and 10 mg./l. of LSD was administered to the human leukocyte cultures 24 and 48 hours before harvesting. The techniques used in the three experiments are described and a table of all three sets of results is given. No chromosomal damage in the root tips of the plant was found and the mitotic activity appeared to be unaffected. The frequency of chromosomal aberrations in the hamster cells was not influenced. However, the mitotic activity was affected, particularly for the 48 hour treatment with 20 mg./l. of LSD. Lastly, there was no increase in the frequency of gaps found in the LSD treated leukocyte cultures. The authors concluded that LSD was not a chromosome breaking agent.

219. Taeusch, H. W., Jr., Carson, S. H., Wang, N. S., and Avery, M. E.
HEROIN INDUCTION OF LUNG MATURATION AND GROWTH RETARDATION IN FETAL RABBITS.
Journal of Pediatrics, 82(5): 869-875, 1973.
E - res. pap. - in vivo - rabbits - teratogenicity - exper. admin. - injection - extended use - female consumpt. - fetal maldevel. - birth, pre term. B-2855.

Two experiments were done to determine the effects of heroin on fetal growth rate and on lung maturation. In the first, seven pregnant rabbits were intravenously injected with 3 to 12 mg. of heroin from day 24 through 26 of gestation. A comparable control group was injected with sterile saline. In the second experiment with seven doses, 2 to 3 fetal rabbits per litter were directly injected intramuscularly with 10 to 20 mg./kg. of heroin through the intact uterine wall on day 24 of gestation. All the females were sacrificed on day 27 and the fetuses were removed stillborn and with airless lungs. The significantly different mean fetal body weights of the experimental and the control groups were 23.1 and 25.3 gms., respectively. The fetuses injected directly with heroin weighed less

than the saline injected fetuses in 12 out of the 16 matched pairs. This difference was not significant. The lungs of the heroin injected fetuses were approximately 70 percent more distensible than those of the saline injected fetuses. Similarly, lungs of the heroin injected fetuses retained 30 to 100 percent more air on deflation to low transthoracic pressures. Both these findings were statistically significant. Lung weight/body weight ratios were increased in both treatment groups. Heroin increased fetal lung maturation and decreased fetal body weight in fetal rabbits.

220. Taska, R.
LSD-DMT-STP.
Texas Medicine, 68(7): 94-98, 1972.
E - gen. pap. - gen. disc. - review - hamsters - mice - rats - chromosome damage - teratogenicity - exper. admin. - intent. use - therapeut. use - chrom. aberr. - congenit. defects - carcinogen. effect - no effect - confound. agent. - drug action B-2856.

A general paper is presented which largely concentrates on the chromosome damaging effects of LSD. The results of nine in vitro studies are reviewed, six reporting some degree of chromosomal damage and the other three failing to confirm these findings. However, five of the former studies used dosages which far exceeded the range of human dosages and it was found that the effects were not greater than those caused by commonly used substances such as antibiotics, and aspirin. The shortcomings of illicit LSD in vivo studies are listed. These include the unreliability of the information concerning the actual drug used, actual dosage, frequency of and total exposure, and the interval since the last exposure; the fact that most LSD users are multiple drug users; and lastly, the fact that the experimental group is more likely to have experienced malnutrition and viral infections. Only three of 18 in vivo studies with LSD found an increased incidence of chromosome damage. Furthermore, one of these three experiments found that the increase in the frequency of damage returned to the equivalent rate before the injection of LSD. There was no definite evidence that LSD was a carcinogen. From the research, it was concluded that LSD was a weak mutagen, effective only with extremely high doses. There was no definite evidence that LSD was a carcinogen or that the pure drug caused human birth defects. LSD was only a weak mutagen, effective only with extremely high doses. The drug action of both dimethyltryptamine (DMT) and 2, 5 dimethoxy-4-methyl amphetamine (STP) was briefly discussed.

221. Titus, R. J.
LYSERGIC ACID DIETHYLAMIDE: ITS EFFECTS ON HUMAN CHROMOSOMES AND THE HUMAN ORGANISM IN UTERO. A REVIEW OF CURRENT FINDINGS.
International Journal of the Addictions, 7(4): 701-714, 1972.
E - gen. pap. - review - tables - humans - chromosome damage - teratogenicity - intent. use - therapeut. use - single dose - extended use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - no effect B-2857.

A review of the literature is presented in which the in vitro and in vivo techniques of research were compared, a previous review on the chromosome damaging effect of LSD by Smart and Bateman was discussed, and the results of in vitro and in vivo studies since 1968 were examined. Most of the later studies used the in vivo approach and found no correlation between LSD usage and chromosomal abnormalities while the in vitro studies did find a positive correlation. Tables of the results of studies discussed are provided. One study by Gilmour et al. found that there were chromosomal aberrations in a large number of drug-using subjects who did not take LSD. The speculation was that the damage could have been the result of other drugs or a combination of drugs, rather than LSD alone. The studies dealing with the effects of LSD on pregnancy and children in utero were outlined. Case reports of infants born to parents who had used LSD before and during pregnancy were presented. This type of investigation is very important in that LSD could be affecting both the mother and the unborn child. Generally, the studies reviewed showed that LSD causes little damage to the chromosomes of the lymphocytes. However, there is evidence to support the contention that LSD may have adverse effects on the normal development of the unborn child.

222. Tjio, J. H., Pahnke, W. N., and Kurland, A. A.
LSD AND CHROMOSOMES. A CONTROLLED EXPERIMENT.
Journal of the American Medical Association, 210(5): 849-856, 1969.
E - res. pap. - in vivo - tables - humans - chromosome damage - exper. admin. - therapeut. use - oral admin. - single dose - extended use - female consumpt. - male consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2858.

Three experiments are reported in this research paper. In the first, the oral dosage ranged from 50 μg. to 450 μg. of LSD. The chromosome preparation techniques are discussed and the time of sampling and the results are given in a table. There was no significant increase in the rates of chromosomal damage after the ad-

ministration of LSD to 32 patients. Only seven out of the 32 patients had not suffered from an upper-respiratory tract viral infection or had not received any drug for four weeks before the pre-LSD sampling. The before and after findings in these patients were not significantly different. The five subjects in the second experiment had used illicit LSD from 4 to 36 times before they were given LSD experimentally. Each subject received LSD at least twice, at dosages of 1 or 2 μg./kg. Again, there was no significant difference between the before and after rates of chromosome damage. In the last experiment, pure LSD was administered from 1 to 26 times to eight normal subjects. The post-LSD chromosomal aberration rate did not exceed the pre-LSD rate found in the patient population. Pure LSD did not damage chromosomes in human white blood cells in vivo.

223. Tjio, J. H., Pahnke, W. N., and Kurland, A. A.
PRE- AND POST-LSD CHROMOSOMAL ABERRATIONS: A COMPARATIVE STUDY.
Advances in Biochemical Psychopharmacology, 1: 191-204, 1969.
E - res. pap. - in vivo - tables - humans - chromosome damage - exper. admin. - therapeut. use - oral admin. - single dose - female consumpt. - male consumpt. - chrom. aberr. - no effect - chrom. analysis, peripheral B-2859.

An experiment is described in which 32 patients were orally administered from 50 to 450 μg. of LSD. Pre- and post-blood samples were taken. A description of the chromosome preparation techniques is given. All slides were scored on a blind basis and at least 200 metaphases were analysed for each culture. The results are presented in a table. It was found that there was no significant difference between the pre- and post-LSD rates of damage in any of the subgroups or in the total patient group, as a whole. Two patients, that could be examined again, of three subjects, which showed a significant increase in the frequency of chromosome damage between the two samplings, had rates which had returned to normal when third samplings were scored. At the same time, LSD was administered from one to 26 times under medical supervision to 8 normal subjects. The post-LSD chromosomal aberration rate did not exceed the pre-LSD rate found in the patient population. Pure LSD did not cause chromosomal damage in the chromosomes of human white blood cells in vivo.

224. Tobin, J. M., and Tobin, J. M.
MUTAGENIC EFFECTS OF LSD-25 IN DROSOPHILA MELANOGASTER.
Diseases of the Nervous System, 30(2): 47-52, 1969.
E - res. pap. - in vivo - tables - fruit flies - chromosome damage - exper. admin. - oral admin. - injection - single dose - male consumpt. - chrom. aberr. - no effect B-2860.

This experiment with Drosophila melanogaster was preceded by a short review on the mutagenic and teratogenic effects of LSD in humans. The authors discuss sex-linked recessive lethals and chromosome aberrations and concluded from the research with Drosophila melanogaster that detection of lethal frequency was more sensible and practicable than attempting to quantitate chromosome breaks. A preliminary experiment in which LSD was injected into fruit flies and in which a Y chromosome break test and a sex-linked recessive lethal test were used, failed to show any significant effects. Then, ten males, which as larvae had been fed 16.7 mcg./ml. of LSD, were selected for individual mating with three females of known genetic composition. The subsequent mating of the offspring was carried out such that the absence of a wild type sterile male in the F2 generation indicated that the F1 male was a carrier of a lethal gene. If a sterile wild type male was absent in the F3 generation, then the F1 female carried a mosaic lethal. No lethals were found in 962 F2 flies and in 772 F3 flies examined. LSD was not a chemical mutagen in the Drosophila melanogaster.

225. Tonge, S. R.
PERMANENT ALTERATIONS IN CATECHOLAMINE CONCENTRATIONS IN DISCRETE AREAS OF BRAIN IN THE OFFSPRING OF RATS TREATED WITH METHYLAMPHETAMINE AND CHLORPROMAZINE.
British Journal of Pharmacology, 47(2): 425-427, 1973.
E - res. pap. - in vivo - tables - rats - teratogenicity - exper. admin. - oral admin. - extended use - female consumpt. - male consumpt. - embryo. maldevel. - fetal maldevel. - autop. - birth, full term B-2861.

Groups of female and male rats were given either 80 mg./l. of methylamphetamine, 200 mg./l. of chlorpromazine, or both of these drugs in their drinking water. Four weeks after the treatment began, the rats were mated within their own groups and the males were removed two weeks later. The females continued to receive the treatment during gestation and the suckling period. The male offspring were killed 3, 6, and 9 months after weaning. The dissection procedure used to separate the cortex, hippocampus,

atriatum, thalamus, hypothalamus, corp. quad., pons/medulla, and the amygdala region of the brains of the offspring is given in detail. Determinations of noradrenaline, dopamine, and normetanephrine were carried out. Methylamphetamine and/or chlorpromazine administration during pregnancy and suckling produced changes in the catecholamine concentrations in the brains of the male offspring that did not differ at different ages of the offspring. The changes appeared principally in the noradrenaline concentrations and it could be possible that the whole metabolism of noradrenaline may be disturbed. In some areas of the brain, it appeared as if the two drugs had antagonistic effects.

226. Tonge, S. R.
PERMANENT ALTERATIONS IN 5-HYDROXYINDOLE CONCENTRATIONS IN DISCRETE AREAS OF RAT BRAIN PRODUCED BY THE PRE- AND NEONATAL ADMINISTRATION OF METHYLAMPHETAMINE AND CHLORPROMAZINE.
Journal of Neurochemistry, 20: 625-627, 1973.
E - res. pap. - in vivo - tables - rats - teratogenicity - exper. admin. - oral admin. - extended use - female consumpt. - male consumpt. - embryo. maldevel. - fetal maldevel. - autop. - birth, full term B-2862.

Groups of male and female rats were given either 80 ml./l. of methylamphetamine, 200 mg./l. of chlorpromazine, or both of these drugs in their drinking water. Four weeks after the treatment began, the rats were mated within their own groups and the males were removed two weeks later. The females continued to receive the treatment during the gestation and suckling period. The male offspring were killed 3, 6, and 9 months after weaning. Determinations of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid levels in the contex, hippocampus, atriatum, thalamus, hypothalamus, corpora quadrigemina, pons and medulla, and the amygdaloid of the brains were made. The results are presented in tables. Chlorpromazine increased 5-hydroxytryptamine concentrations in the cortex and hippocampus only, and decreased them in the hypothalamus and pons/medulla. It also appeared that the two drugs had antagonistic effects in different areas of the brains.

227. Truhaut, R., and Deysson, G.
ABSENCE D'EFFET DU DIÉTHYLAMIDE LYSERGIQUE SUR LES CHROMOSOMES DANS LES CELLULES MÉRISTÉMATIQUES RADICULAIRES D'ALLIUM SATIVUM L. [Absence of lysergic diethylamide effect on the chromosomes in Allium sativum L. meristematic radicular cells.]
Comptes Rendus Hebdomadaires des Séances de L'Académie des Sciences; (D): Sciences Naturelles, 270: 1165-1166, 1970.
F - res. pap. - in vivo - plants - chromosome damage - exper. admin. - single dose - chrom. aberr. - no effect - chrom. analysis B-2863.

Further experiments were performed on the effects of LSD on chromosome structures. The authors studied the effects of various concentrations from .1 to 80 mg. of LSD/100 gm. for up to 7 days of exposure on the root stems of Allium sativum L. For each experimental condition, 500 metaphases were studied in each of 10 meristems. No significant effect on the mitotic activity or on the frequency of chromosomal alterations were noted.

228. Uyeno, E. T.
EFFECTS OF PRENATALLY ADMINISTERED LYSERGIC ACID DIETHYLAMIDE ON THE VIABILITY AND BEHAVIORAL DEVELOPMENT OF RAT OFFSPRING.
In: Committee on Problems of Drug Dependence. Report of the Thirty-second Meeting, 16-18 Feb., 1970, Washington, D. C. pp. 6550-6555, 1970.
E - book - in vivo - rats - teratogenicity - exper. admin. - s. c. admin. - single dose - female - consumpt. - fetal maldevel. - fetocidal - no effect B-2864.

Groups of pregnant rats were put into one of four groups receiving either 2, 4, or 6 mg./kg. of LSD or receiving a saline injection on the 4th day of gestation. The offspring were weighed and the total number of abnormal offspring recorded. There was no significant difference between the percentages of stunted and stillborn offspring in the different groups. However, the percentages of nonproductive females in the LSD treated groups were significantly greater than in the control group. This effect was dose related with the ED_{50} being about 4.76 mg./kg. of LSD. Six offspring from each group were sacrificed for a study of their brains. No differences were noted in the number of lesions or to do with the cells, fibers, and blood vessels of the brains. The rest of the offspring were administered the spontaneous activity test, the one-path Lashley maze, a shock-avoidance test, and a food competition test. In addition, ten males and ten females from each group were

mated to a new group of animals. The experimental offspring were no different from the controls in the activity and learning tests. There was also no difference in the sexual potency test.

229. Uyeno, E. T.
LYSERGIC ACID DIETHYLAMIDE IN GRAVID RATS.
Proceedings - Western Pharmacology Society, 13: 200-203, 1970.
E - res. pap. - in vivo - tables - rats - teratogenicity - exper. admin. - s. c. admin. - single dose - congenit. defects - no effect - birth, full term B-2865.

Eighty-four females that had delivered normal size litters and had successfully raised their young were assigned to one of three experimental groups receiving either 2. 5, 5, or 10 μg. /kg. of LSD on the 4th day of gestation or were placed in the control group. The offspring were weighed and the total number of abnormal offspring were recorded. Fifteen offspring from each group were sacrificed for a histological study of their brains. The rest were given the spontaneous activity test, the one-path and two-path Lashley maze, a shock-avoidance test, and a food competition test. The percentages of nonproductive females in the experimental groups were not significantly different from that in the control group. There were no significant differences in the percentages of stunted and of stillborn offspring. Microscopic examinations of the brains of the sacrificed offspring revealed no significant differences between the experimental animals and the controls. In addition, there were no significant effects on the behavioral development of the offspring. In an attempt to replicate the findings of Alexander et al. rats from the same strain and obtained from the same supplier were subcutaneously injected with 5 μg. /kg. of LSD on the 4th day of gestation. The present investigations found no teratogenic effects in the offspring and failed to obtain results similar to those of the previous experimenter.

230. Vann, E.
LETHAL MUTATION RATE IN DROSOPHILA EXPOSED TO LSD-25 BY INJECTION AND INGESTION.
Nature, 223: 95-96, 1969.
E - gen. pap. - in vivo - fruit flies - chromosome damage - exper. admin. - oral admin. - injection - single dose - extended use - male consumpt. - dose/response - stage of devel. - chrom. aberr. - chrom. analysis B-2866.

Groups of male fruit flies, 36 to 48 hours old, were injected with either 24 or 470 μg. /g. of LSD. Groups of 24 hours old males were

orally administered either 420 or 8,460 μg./g. of LSD. Comparable control groups were provided. For each treatment, twenty fertile males were mated to virgin females every three days for a total of three broods each. About 30 paternal X or second chromosomes were isolated and examined from each of the three broods arising from each male, giving a total of 90 chromosomes. The two methods used for the detection of lethal mutations were the Muller-5 and the Curly-Lobe/Plum techniques. Tables of the results were given. There was some indication that there was a threshold dose-response for the mutagenic action of LSD in Drosophila. Only the higher concentration of 2,000 μg./ml. caused a significant increase in the frequency of recessive lethals. The author discussed the results of previous research which supported this contention. Lethals were induced by both injection and ingestion, however, the relative efficiencies of induction were quite different. It was concluded that ingestion was not as efficient a method of exposure as was injection.

231. Vann, E., Matlen, C., and Rossmoore, H.
GENETIC EFFECTS OF LSD-25 ON E. COLI.
Mutation Research, 10(4): 269-275, 1970.
E - res. pap. - in vivo - plants - chromosome damage - exper. admin. - single dose - dose/response - chrom. aberr. - chrom. analysis B-2867.

The genetic effects of LSD on E. coli were studied using a technique in which equilibria between wild and mutant cells in culture were used to estimate the mutation rate. Wild type E. coli cells were treated with varying concentrations of LSD from 0.01 mg./ml. to 1.2 mg./ml. The experimental cultures were limited to initial volumes of 20 ml. It was found that when LSD was added at concentrations greater than 0.1 mg./ml., mutation rates were significantly higher than the spontaneous level. It was found that there was a linear relationship between dose and response. For each 0.1 mg./ml. increment of LSD, the mutation rate increased by .0001 percent over the spontaneous rate. There was a relatively low threshold, if any. In addition, there was a real difference between the experimental and the control generation times. Further observation made it seem most plausible that the origin of the new mutants was directly dependent upon cell division.

232. Wagner, T. E.
IN VITRO INTERACTION OF LSD WITH PURIFIED CALF THYMUS DNA.
Nature, 222: 1170-1172, 1969.

E - gen. pap. - in vitro - mammals - chromosome damage - exper. admin. - chrom. aberr. - hypothesis B-2868.

A spectropolarimeter with a dichroism attachment showed the circular dichroism spectra of calf thymus DNA solutions with and without LSD. The effects of LSD were compared with the known intercalater, ethidium bromide. Marked changes in the ultraviolet circular dichroism spectrum of DNA was observed when LSD was added to give a ratio of 1/2 LSD to DNA. The results supported the contention that LSD may intercalate within the DNA helix causing changes in the conformation of the DNA, much as ethidium bromide does. It was suggested that this intercalation could cause the dissociation of histones, which might render the chromosomal DNA susceptible to enzymatic attack and breakage.

233. Walker, F. A., and Helz, T.
PRESUMPTIVE TERATOGENICITY OF "STREET" LSD.
Journal of Pediatrics, 78(6): 1059, 1971.
E - abst. - case rep. - humans - chromosome damage - teratogenicity - intent. use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - chrom. analysis B-1744.

Three children, born to parents who later gave histories of drug use, were found to suffer a syndrome of hypoplastic ears, short neck, syndactyly of the third and fourth fingers, and hypoplastic genitals. Chromosome analysis confirmed the diagnosis of nosaic triploidy. An unusual breakage pattern affecting the short arm of a "B" chromosome was noted. There could possibly have been a fourth case in which the pregnancy was spontaneously aborted.

234. Warkany, J., and Takacs, E.
LYSERGIC ACID DIETHYLAMIDE (LSD): NO TERATOGENICITY IN RATS.
Science, 159(3816): 731-732, 1968.
E - gen. pap. - in vivo - rats - teratogenicity - exper. admin. - i. p. admin. - oral admin. - extended use - female consumpt. - congenit. defects - fetal maldevel. - resorpt. rate - no effect - birth, pre term. - birth, full term B-2869.

Fifty-five pregnant rats were administered LSD either intraperitoneally or orally in single doses on the 7th, 8th, or 9th day of gestation or in multiple doses from the 7th to the 12th day of gestation for a total dosage to individual rats of from 1. 5 to 300 μg. of LSD. Four litters were completely resorbed. Forty-seven females were sacrificed on the 21st day of gestation and four were allowed to

deliver and raise their young. Of the 508 21-day fetuses, only four were considered abnormal with one having hydrocephalus, the second having short extremities and syndactylism and the others being stunted. The four females allowed to deliver, had 44 normal offspring. The experiment showed that LSD was not teratogenic in rats even with doses as high as 300 μg.

235. Warren, R. J., Rimoin, D. L., and Sly, W. S.
LSD EXPOSURE IN UTERO.
Pediatrics, 45(3): 466-469, 1970.
E - gen. pap. - case rep. - tables - humans - male - chromosome damage - teratogenicity - intent. use - oral admin. - extended use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - premature birth - no effect - birth, full term - chrom. analysis B-2870.

A case report is provided of a perfectly normal boy born to parents who had ingested pure LSD, consumed peyote, and smoked cannabis regularly before and during the first 4 months of pregnancy. Each parent took roughly 300 to 1000 μg. of LSD every 3 or 4 weeks until the mother realized that she was pregnant. The child was born two weeks prematurely and was judged to be completely normal. Leukocyte cultures were started on both parents and the child five weeks after the father had ingested 800 μg. and the mother had taken 320 μg. of LSD. It was found that there were no abnormal chromosomal forms or a significant number of breaks. The only unusual cytological finding was a large number of micronuclei scattered individually and in groups in the blood cells of the father.

236. Whitmore, F. W.
CHROMOSOMAL EFFECT AND LSD: SAMPLES OF FOUR.
Science, 162: 1508-1509, 1968.
E - lett. ed. - gen. disc. - humans - chromosome damage - intent. use - chrom. aberr. - no effect B-2871.

The writer discusses the statistical aspects of a study done by Sparkes et al. in which it was found that there was no significant difference in the frequency of chromosomal aberrations in users of LSD and nonusers. Although the researchers covered the risk of rejecting their hypothesis if it was true, there was also the risk of accepting a false hypothesis. From his statistical analysis, the writer determined that there was a greater than 25 percent chance of the researchers accepting the hypothesis that there was no difference between the users and nonusers. This was a rather high risk which should be reduced in further research. This could be

done by increasing the replications in each of the experimental groups used in the experiment.

237. Yielding, K. L., and Sterglanz, H.
LYSERGIC ACID DIETHYLAMIDE (LSD) BINDING TO DEOXYRIBONUCLEIC ACID (DNA).
Proceedings of the Society for Experimental Biology and Medicine, 128: 1096-1098, 1968.
E - res. pap. - in vitro - mammals - plants - chromosome damage - exper. admin. - chrom. aberr. B-2872.

An in vitro experiment was done in which the spectra of solutions of LSD and 2-Br-LSD containing varying concentrations of DNA were recorded. When native calf thymus DNA was added, the absorbance spectra of the solutions progressively decreased at 310 mμ. The DNA had a similar effect on the fluorescence emission spectra of the solutions. Since similar effects were found with the solution of 2-Br-LSD, it was concluded that the binding to DNA was a general property of this group of drugs. Yeast RNA was added to these solutions and negative findings were found. No changes in the spectra were found when nonhelical DNA was added. It appeared as if LSD attached primarily to the helical DNA. The addition of $MgCl_2$ to the drug-DNA mixture reduced the spectral change produced by the DNA. This effect could have been due either to the effect of $MgCl_2$ on the DNA helix or to interference with an electrostatic attraction between the DNA-phosphate and the drug. Binding was also decreased by the prior heating of the DNA.

238. Zellweger, H., McDonald, J. S., and Abbo, G.
IS LYSERGIC-ACID DIETHYLAMIDE A TERATOGEN?
Lancet, 2(7525): 1066-1068, 1967.
E - gen. pap. - case rep. - humans - female - chromosome damage - teratogenicity - intent. use - oral admin. - extended use - female consumpt. - male consumpt. - chrom. aberr. - congenit. defects - birth, full term - chrom. analysis, peripheral B-2873.

A girl, who was born to parents who had ingested LSD on several occasions during the mother's pregnancy, suffered from a malformation of the right leg. The mother had taken the drug on the 25th day and three times between the 45th and the 98th days after her last menstrual period. The baby was born seven days later than expected and was normal, otherwise. The malformation was characteristic of the unilateral fibular aplastic syndrome, and included the absence of the fibula, the anterior bowing of the shortened tibia, the absence of the lateral rays of the foot, the shortening

of the femur, and the dislocation of the hip. A total of ten chromatid breaks and one polyploidy were found in the peripheral white blood cells of the parents and the child. Since the mother's second dose of LSD was taken during the critical period for the production of leg deformities, it did not appear unreasonable to suspect a causal relationship between the use of LSD and the malformation. Lastly, three cytogenetic and/or teratogenic complications of LSD use are listed.

239. Zellweger, H., McDonald, J. S., and Abbo, G.
IS LYSERGIDE A TERATOGEN?
Lancet, 2: 1306, 1967.
E - lett. ed. - gen. disc. - humans - chromosome damage - teratogenicity - intent. use - oral admin. - chrom. aberr. - congenit. devects - no effect - chrom. analysis, peripheral B-2874.

The authors explain in more detail the chromosome analyses performed on the parents and child reported in a previous paper concerning the presence of the unilateral fibular aplastic syndrome in a child born to parents who had ingested LSD. Approximately eight percent of the cells of the parents and the child showed chromatid breaks compared with only 3. 5 percent of the cells of normal controls. Further examination of the skin fibroblasts of the father revealed chromatid interchanges such as triradial and quadriradial structures.

240. Zelson, C., Rubio, E., and Wasserman, E.
NEONATAL NARCOTIC ADDICTION: 10 YEAR OBSERVATION.
Pediatrics, 48(2): 178-189, 1971.
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During the years 1960 through 1969, 384 children born to 382 heroin addicted mothers were observed in a hospital in New York City. Forty-nine percent of these children were under 2,500 gm. in weight at birth. This compared to the average premature infant birth rate of 14. 9 percent found in the same hospital. Sixty-seven percent developed signs of withdrawal within the first 4 days of life and 68. 7 percent of these required treatment for their symptoms. Tables recording all the clinical data are provided. The mortality rate among these infants was high. Nine of the 14 deaths occurred within 9 hours of birth. Two died as a result of congenital abnormalities and respiratory distress. Seven infants were in severe

respiratory distress from birth but there was no evidence of Hyaline membrane disease at autopsy. In addition, three infants died after their discharge from hospital. Only four infants were born with major congenital anomalies. One had a congenital heart lesion, one had multiple anomalies including a tracheoesophageal fistula, one had arthrogryposis multiplex, and the fourth had incontinenti pigmenti. Seven other infants developed inguinal hernias in the immediate newborn period. The withdrawal symptoms found in some of these newborns, their correlation to the length of maternal addiction, the presence of morphine and quinine in the urines of the newborns, and the fact that chlorpromazine is well tolerated in the newborns of narcotic addicts are discussed.

241. Zetterberg, G.
LYSERGIC ACID DIETHYLAMIDE AND MUTATION.
Hereditas, 62(1-2): 262-264, 1969.
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The growth of Ophiostoma multiannulatum, an ascomycete, was tested in culture in which LSD was added. The strains used had a yeast like growth and morphology. Biochemical mutants can be induced by ultraviolet light, X-rays, and many chemicals. A cell suspension containing 50 mg./l. of LSD was shaken for 13 hours, washed, and plated on complete medium. LSD treatment did not induce forward mutations. In the back-mutation test with cells of the arginine-less mutant, LSD proved non-toxic, did not affect growth rate, and had no significant influence on the frequency of back-mutations in this strain of Ophiostoma multiannulatum.

APPENDIX: Selected Related Citations

A list of citations dealing with teratogenic and chromosomal damaging effects of licit drugs.

1. Aleksandrov, V. A.
CHARACTERISTICS OF THE DISTURBANCE OF EMBRYOGENESIS UNDER THE EFFECT OF MYELOSAN IN THE EARLY STAGES OF RAT DEVELOPMENT.
Bulletin of Experimental Biology and Medicine, 61(4): 423-426, 1966.
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2. Apgar, V.
DRUGS IN PREGNANCY.
Journal of the American Medical Association, 190(9): 840-841, 1964.
E - gen. pap. - gen. disc. - tables - humans - teratogenicity - therapeut. use - extended use - female consumpt. - congenit. defects - death - fetocidal - no effect - birth, full term B-2878.

3. Arora, O. P., Shah, V. C., and Rao, S. R. V.
STUDIES ON MICRONUCLEI INDUCED BY MITOMYCIN-C IN THE ROOT CELLS OF VICIA FABA.
Experimental Cell Research, 56: 443-448, 1969.
E - res. pap. - in vivo - plants - chromosome damage - exper. admin. - chrom. aberr. - chrom. analysis B-2879.

4. Auerbach, C.
THE CHEMICAL PRODUCTION OF MUTATIONS. THE EFFECT OF CHEMICAL MUTAGENS ON CELLS AND THEIR GENETIC MATERIAL IS DISCUSSED.
Science, 158(3805): 1141-1147, 1967.
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THE EFFECTS OF DRUGS ON THE FOETUS.
Pharmacological Reviews, 12(1): 37-90, 1960.
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6. Baranov, V. S.
CHARACTERISTICS OF THE TERATOGENIC EFFECT OF AMINOPTERIN COMPARED WITH THAT OF OTHER TERATOGENIC AGENTS.
Bulletin of Experimental Biology and Medicine, 61(1): 77-81, 1966.
E - res. pap. - in vivo - tables - rats - teratogenicity - exper. admin. - injection - extended use - female consumpt. - dose/response - stage of devel. - congenit. defects - embryocidal - embryo. maldevel. - birth, pre term. B-2882.

7. Barrow, M. V.
A BRIEF HISTORY OF TERATOLOGY TO THE EARLY 20TH CENTURY.
Teratology, 4(2): 119-129, 1971.
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8. Bauchinger, M., Schmid, E., Pieper, M., and Zöllner, N.
ZYTOGENETISCHE WIRKUNG VON CYCLAMAT IN MENSCHLICHEN PERIPHEREN LYMPHOZYTEN IN VIVO. [Cytogenetic effect of cyclamate on human peripheral lymphocytes in vivo.]
Deutsche Medizinische Wochenschrift, 95: 2220-2223, 1970.
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9. Becker, B. A., and Gibson, J. E.
TERATOGENICITY OF CYCLOHEXYLAMINE IN MAMMALS.
Toxicology and Applied Pharmacology, 17: 551-552, 1970.
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New England Journal of Medicine, 282: 225, 1970.
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12. Bishun, N. P.
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Mutation Research, 11: 258-260, 1971.
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Journal of Clinical Pharmacology, 12(2-3): 61-70, 1972.
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Naunyn-Schmiedebergs Archiv für Experimentelle Pathologie und Pharmakologie, 249(2): 117-145, 1964.
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RESPONSE OF CHROMOSOMAL PUFFS TO CRYSTALLINE HORMONES IN VIVO.
Proceedings of the Society for Experimental Biology and Medicine, 131: 209-213, 1969.
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CHROMOSOME ANOMALIES AS A CAUSE OF SPONTANEOUS ABORTION.
American Journal of Obstetrics and Gynecology, 97(3): 283-293, 1967.
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Lancet, 2(7520): 830-831, 1967.
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Biochemical Pharmacology, 18(5): 1147-1156, 1969.
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Proceedings of the National Academy of Sciences, 50: 16-24, 1963.
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Diabete, 19: 215-221, 1971.
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Humangenetik, 9: 281-285, 1970.
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REPRODUCTION AND TERATOLOGY STUDIES ON PROPOXYPHENE NAPSYLATE.
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Archivio Putti di Chirurgia Degli Organi di Movimento, 23: 413-422, 1968.
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Food and Cosmetics Toxicology, 8: 617-623, 1970.
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